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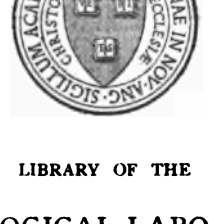


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# TEXT-BOOK OF
# GENERAL PATHOLOGY

# A TEXT-BOOK OF GENERAL PATHOLOGY

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OF

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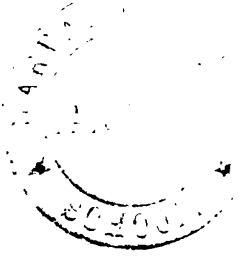


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A

# PREFACE

In modern times physiology and pathology had a common starting-point in the doctrine of the cell as the ultimate unit of the animal body; but, nevertheless, they tended for many years to diverge. Physiology was concerned chiefly with certain specialized functions of cells, the phenomena of which hardly touch the problems of disease, and was hampered in its progress by the backward condition of such ancillary sciences as chemistry and physics. Pathology, greatly influenced by anatomy, was engaged with the observation of results rather than the elucidation of the underlying vital processes. Within recent years, however, the two sciences have converged again, for not only has the scope of physiological inquiry regarding the intimate processes of cellular life been broadening, but pathology, in recording such phenomena as those of perverted secretion or the effects of morbid cellular life on normal functions, has opened up new lines of inquiry for the physiologist. Disease, in fact, has often supplied physiological experiments far more delicate than any that could be performed in the laboratory. There is thus at present a constant interaction of the two sciences; the way has thus been opened up for the elucidation of the doctrine often foreshadowed by the older pathologists that the laws of disease are really the laws of health, and lack of co-ordination between the normal activities of the component tissues of the body is often the most important factor in the origin of disease.

Although the establishment of these principles is still very incomplete, it has seemed to the editors of this book that the time has come for another attempt to present, as far as it may be possible, the results obtained by the two sciences in working at the problems of disease. In many branches of the subject the combined efforts have as yet had little effect, and in the treatment of these it has been necessary to follow conventional lines; but in others new light

has been shed on the problems of disease by the adoption of the physiological standpoint, and an endeavour has been made to set forth the bearings of the new knowledge thus available.

Representatives of physiology, pathology, and medicine are found among the contributors of the various chapters. The authors are individually responsible for the views expressed in their articles, and no attempt has been made by the editors to prevent the appearance of any divergent views, which may be found in different portions of the work.

The book is intended for the use of the advanced student and the practitioner, and, as both classes from their studies in practical pathology are familiar with ordinary histological details, the illustrations have been confined to the elucidation of less familiar points.

The editors wish to thank Dr. Candler for the great assistance he has rendered to Drs. Mott and Sewell, and also Drs. Haldane and Kennaway for their help with suggestions, criticisms, and corrections in relation to some of the articles.

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# GENERAL PATHOLOGY

## CHAPTER I

## INTRODUCTION

By J. RITCHIE and M. S. PEMBREY

The province of general pathology is to correlate the processes in the diseased with those in the healthy; to determine the causes of failure in the interdependence of the different parts of the body; to show how the failure of one tissue reacts on all the other tissues; and, by following the progress of disease, to explain how it causes death. In short, general pathology is the study of disease from the physiological point of view.

It is impossible to draw a hard-and-fast line between physiology and general pathology, for in most cases there are no definite signs to indicate when health ends and disease begins. The condition of health has two aspects—a subjective and an objective. Subjectively a man associates the term "health" with the capacity of passing with a sense of well-being through a constantly-recurring cycle of activity and rest. From the objective standpoint, the healthy body has been considered as an efficient machine, and its capacity for transforming energy has been expressed in physical terms. In many respects, however, the comparison of the body with a machine is misleading: the healthy body grows stronger and more efficient with work; it feeds itself and removes its own waste; it repairs damaged parts, and possesses a most extensive range of adaptation to different kinds of work. The comparison with a machine leaves out of account such fundamental characteristics as sensation, growth, and reproduction.

Attempts have been made to formulate a conception of health on a statistical basis by establishing standards of average capacity. On such a basis health would be defined as the condition of the individual which most closely approached to the average standard of the race. The possession of health, however, is so frequently associated with a wide departure from such an average that such a method becomes useless, and the subjective sensation forms the only satisfactory means of judging of the existence of health.

It has long been a matter of experience that the loss of the feeling

of health is usually associated with alterations in structure, and, although such alterations may be present before the subjective sensation is affected, ultimately in all cases they appear. These alterations constitute the changes which come under the province of morbid anatomy, and form the basis on which the clinician rests his judgments regarding disease. In the early development of knowledge of disease, only gross alterations in the structure of the body could be recognized; but towards the middle of the last century the cellular pathology arose, and a better understanding of the nature of such gross changes was obtained by the recognition that they represented, in mass, changes occurring in the cellular units of the body.

The study of morbid anatomy resulted in three great groups of alterations in structure being determined. Firstly, changes which were denominated "degenerations"; secondly, the occurrence of proliferation of cells in response to so-called "irritants"; and, thirdly, the initiation, under undetermined conditions, of cellular proliferations of unknown origin, which were denominated "new growths" or "tumours." Whether all departures from health are associated with changes in structure is still a matter of opinion, but as microscopic technique has been elaborated and improved it has become almost certain that such changes in structure do occur in every case. The unification of the processes at work in disease, which the progress of knowledge has brought about, also forms the basis for the conception that in many, if not in all, cases these processes can be looked upon as a further development of characteristics which are essential to the normal life of the cell. Disease, thus, does not depend on the development of any new properties in protoplasm. It rather results from an interference in the correlation between the different activities of living matter which constitutes the state of health.

The morphological unit of all living organisms from the protozoa upwards is the cell; and whether the components of an organism consist of one or of many such units, certain general properties are associated with all cellular life. Of these, excitability, metabolism, growth, and reproduction, are generally recognized. Not so obvious, however, are the facts that the capacity for function in a cell is never indefinite or continuous—at any rate, at the same level of efficiency—and that, when regeneration by means of union with another cell is impossible, gradual failure of vital activity and ultimate death are inevitable. Thus, it would appear that even amongst the protozoa an asexual cycle ultimately ends in senility, though the cell may be capable of millions of divisions before this condition supervenes, and though its advent may be long postponed by constant incursions into a fresh environment. Even under apparently normal conditions periods of depression may occur, characterized by cessation of feeding, growth, and reproduction,

and evidenced by changes in the nucleus and by the appearance of fatty granules in the protoplasm. Thus, even the simplest organisms may manifest alternations of activity and rest, and tend to degenerate and die.

The outstanding feature of cellular life, as exemplified in the higher animals, is specialization in destiny and in function—in destiny, in that the reproductive cells are marked off and isolated from the somatic, which now have no opportunity for rejuvenescence through conjugation; in function, in that the latter are separated into groups, each of which is adapted for some special purpose. The organism is no longer a self-contained cellular unit, but a social system. Instead of a single cell manifesting in its vital activity all the fundamental capacities of protoplasm, each function—be it sensitiveness, motility, secretion, or defence—is delegated to a special tissue. Such a division of labour involves two new features—interdependence and inter-regulation—and it follows that, though the whole is more efficient, it is also more complicated and more delicate. The failure of a cell to perform its special function now no longer affects itself alone, but reacts on all the others, and may cause failure of the whole organism of which it is a part. The degree of the complexity of the animal body is now being more and more realized. Further, so impotent are the most advanced methods that we often can speak only of a property of a tissue, without the least knowledge of the nature of the substance with which the property is associated, or of the part which the property plays in normal life. Thus, the blood-plasma of the guinea-pig possesses the property of laking the red blood-corpuscles of the ox, and the property depends on the presence and associated action of two separate qualities; but we know nothing of the part the possession of these qualities plays in the economy of the animal. Nowhere is the complexity of the organism more apparent than in the phenomena of inter-regulation. Not only is there the control exercised by the nervous system, but more than ever is it evident that certain manifestations of cellular activity are only called forth by the chemical secretions of other cells, that the content of the blood in such secretions is kept at a constant, and that, if the amount utilized at any particular moment is increased, there must be a corresponding increase in the functions of the secreting cells. All the facts relating to interdependence and inter-regulation go to indicate the great diversity of opportunity for failure as well as adaptation. There may, for example, be an error in the glycolytic mechanism, and the consequent aberration in the carbohydrate metabolism, on which the energy of so many tissues depends, may mean for them disaster. Even a slight degree of failure of a fundamental chemical reaction may indirectly cause the organism to perish. Again, constant demands made on an organ may lead it into a habit of overproduction, and

a useless expenditure of energy may result in functional failure. Thus, the production of antitoxin by one set of cells may protect the whole body from the pernicious effects of a poison, but the cells very readily form a habit of producing this substance in an amount in excess of all necessary requirements. There is evidence that ultimately they may lose the capacity of responding to a call for secretion. Another possible failure in interdependence lies in the assertion by one tissue of an excessive individualism; it carries on its function to the detriment of the whole. Such an example is found in the evil effects of hyperthyroidism.

It is to be noted that in certain circumstances a failure in interdependence may be to a certain extent compensated. Many bodily tissues hold a reserve of capital in the form of undeveloped embryonic tissue, which under ordinary circumstances is not required, but is available to meet an emergency defect. Such compensation may be perfect, or may be partial and temporary. Under the former we have the capacity of the lymph glands to take up the function of the spleen, of one kidney to do the whole work of the body when its fellow is destroyed, of part of the liver to hypertrophy when another part fails. Of incomplete compensation, the hypertrophy of the heart in valvular incompetence affords the best instance, as it almost invariably is of a temporary character.

While we can only state as facts the occurrence of useless overproduction and the assertion of individualism, we can trace the processes, and sometimes assign the causes of failure of the function of a tissue. During the whole of life somatic cells are being formed, are passing through a stage of active function, and are dying. The extent of this process varies in different tissues. It is most marked in the mother cells of the blood, and, according to present evidence, is only absent in the cells of the central nervous system. In the normal adult body the balance between cellular production and wastage is truly struck. When, by the operation of the natural tendency of protoplasm already alluded to, wastage exceeds production, the body becomes senile. An uncomplicated general senility is a rare event. When the process is general, it is usually secondary to a widespread senility of the arterial system, but in certain centenarians pure cases probably occur. It is characterized by a gradual atrophy of all the bodily tissues. Premature senility, however, either local or general, may come about in a variety of ways. Some of these are quite obscure—for example, the change in the cells of Langerhan's islands in the pancreas, which is associated with diabetes; in other cases excessive stimulation may play a part. The commonest cause of premature senility is starvation or intoxication. The former occurs by the general supply of nutrition being cut off either by the failure of the tissues whose function it is to prepare for consumption the raw food-

supply of the body, or by the local blood-supply being diminished. In intoxication, the chief factor is, probably, the loss of the capacity for assimilation. In both starvation and intoxication, energy for continued function can only come from the cell breaking up that part of its protoplasm set apart for the function peculiar to it. For example, if this takes place in a muscle cell in the presence of sufficient oxygenation, diminution in size—simply atrophy—will result. If oxygenation be imperfect—though in this particular case opinion is not unanimous—less oxidized products, especially fat, will be deposited in the cell. There is in intoxication probably another phenomenon; substances, again especially fat, which are usually absorbed into the cell only in small quantities, are taken up in an excessive amount.

The fate of cells becoming senile varies. In certain cases in superficial tissues, as in the skin, the cells in dying undergo a horny transformation which enables them to protect the more delicate underlying cells; by friction they are removed from the body. In internal parts they may also serve a protective purpose in their death by undergoing a mucous degeneration. On the other hand, diminution in vitality in a cell may lead to its becoming the prey of the phagocytic properties possessed especially by cells of the endothelial type, this process being exemplified by the manner in which the spleen disposes of the leucocytes which have served their purpose. Similar principles govern the disposal of prematurely senile cells. Sometimes these are cast off, sometimes they disintegrate, and sometimes a phagocytic process comes into play, as is seen in the case of the cells of the central nervous system.

The natural process of senility does not, however, represent the only physiological process which may on occasion develop abnormal tendencies. The advent of premature senility is most apt to occur in the cells which exhibit the most specialized function—as, for example, nerve and muscle cells. These tend to exhibit a passivity under changing external conditions. They are, indeed, capable of increased function, but they have more than their less highly specialized relations lost the capacity of manifesting the general protoplasmic capacities of the embryonic cells from which they originally came. There exist in the body, however, many groups of cells which respond to a call for increased function, not only by a greater individual activity, but by increasing the number of productive individuals. Such a process probably occurs even in specialized cells, such as those of the liver; for when the cells of this organ die in any great number, the remaining units not only enlarge, but multiply, and there is evidence that the function of the organ is thereby maintained. The process is, however, specially exemplified in the leucocytes and their mother cells, and in cells of the endothelial type such as are found in the connective tissues, serous membranes, and in the sinuses of the spleen and of lym-

phatic glands. As has been indicated, such cells under ordinary circumstances play an important part in disposing of the products of ordinary cellular disintegration in the body. During the growth of a body they are the agents responsible for such changes as the moulding of bones, and also the removal of parts, such as the tadpole's tail and the umbilical cord, which are useless to the adult. On occasion their capacities for amœboid movement and phagocytosis are much increased, and the increase of the functional capacity of the tissue to which they belong is augmented by the increase of functioning units resulting from their division. Though definite proof of secretion by such cells of substances into the body fluids is still wanting, the possibility of such an occurrence must be kept in mind. The usual stimulus for over-activity on the part of these cells is the incursion into the body of foreign proteins, especially of living foreign protein in the shape of bacteria. Whether the body is constantly on guard against inimical bacterial forces is at present undetermined, but this is a possibility. Whether living protoplasm is constantly actively killing bacteria, or is merely a substance on which bacteria do not find suitable nutriment, it is certain that the cessation of life is at once associated with free bacterial growth in the dead protoplasm. Whatever be the truth regarding such facts, bacteria do from time to time gain entrance to the living body, and a series of processes occur which are usually summed up by the word "inflammation." A characteristic of these is their physiological basis. The vascular phenomena can be referred to the flushing of a part caused by simple friction. Even this, as is well known, may, if persisted in, cause an undue passage of lymph through the vessels, a common example of which is found in a blister. It may even be that such a flushing, due to special circulatory activity or disturbance, may be the cause of the transient albuminuria which follows severe muscular exercise in many healthy adults. Precisely similar phenomena characterize the early action of bacterial *noxæ* on the vessels round a focus of infection. The reactive phenomena of inflammation show an even closer relation to physiological processes, for they are merely exaggerations of the amœboid movement and phagocytic capacity which the cells involved normally manifest. The reaction does not, however, end in increased function alone, but leads to increased multiplication. Thus, a few hours after a serious infection occurs, the leucoblastic cells in the bone marrow are actively dividing, and the young cells are being cast out into the blood. Proliferation of endothelial cells at the scene of infection is also quickly noticeable. Soon, also, the activity of a secretory apparatus of unknown site is evidenced by the augmentation in the body fluids of substances inimical to bacterial life, or of the appearance of such substances not ordinarily present. Previous to, or synchronous with, such events there appear signs of senility and death, it may

be in the original cells, or in those newly formed. These degenerative changes are the insignia of the partial victory of the assailant.

The process of repair is also essentially physiological in basis. The higher animals have lost the capacity possessed by lower forms to replace injured limbs, but the power to fill a gap in continuity is maintained to a limited, yet to a relatively efficient, degree. The embryonic formative power is now chiefly manifested by connective tissues, and in these the primitive processes of fibrous tissue and capillary formation are repeated. When a specialized tissue is wounded, the breach is filled from its supporting framework; but sometimes even here, as happens in a bone, the special characters are reproduced. When an external or internal surface is wounded, the epiblastic or hypoblastic sheets grow over the connective tissue laid down. The process again follows physiological law in that, when the normal shape of the body is attained, cell division comes to an end, as is the case in growth.

This law which regulates growth can at present merely be stated as a fact. We are wholly ignorant of the physical processes which underlie it. We know that the movements of leucocytes are determined by chemotactic influences, and we can imagine that the depletion of the reservoirs of these cells by the concentration of the circulating elements at a focus of infection may stimulate cell division at the fountain-head. This may not be the whole story, and cell division may really be due to the effects of absorption of bacterial products; but, at any rate, in either case we have a working hypothesis. But we have no data for forming a theory of how the wastage from the surface of the skin is absolutely balanced by proliferation in the deep layers of the rete Malpighii, or of the other similar processes which during adult life maintain the different bodily tissues at a constant. As we know nothing of the stimuli and restraints which make all normal cellular division a correlated whole subservient to the good of the social system, we know nothing of the factors underlying the useless proliferation of cells which constitutes a tumour. Little help towards the understanding of the problem comes from the analogies existing between the growth of a new individual *in utero* and that of a parasite using the maternal organism for its own purposes, although the tumours originating from the chorion behave in exactly the same way as tumours originating in the body of the mother herself. All we can say is that in some way cells do from time to time become individualistic, and that tumours, with certain exceptions to be treated of in the section on the subject, arise from tissues which in adult life retain a capacity for multiplication.

While thus most of the processes underlying disease can be traced to a physiological basis, there remains one which stands by itself—namely, the coagulation of the blood, which may occur

*intra vitam.* Although hæmorrhage occurs under physiological conditions in menstruation and parturition, the coagulation of the blood in a wound is in some respects a new event in the animal economy. Though, so far as its advantage to the body is concerned, it may be a product of evolution, this in no way explains its origin. To explain this, we must know on what primitive capacities of protoplasm evolutionary law worked in the development of the phenomenon, and of the physical groundwork here we are entirely ignorant.

Sufficient has, however, been said to show that the three processes of degeneration, reaction, and new growth, can all be looked on as having a basis in processes which are necessary in the normal life of an animal. These processes, especially the first two, lie at the root of all disease, though in any individual morbid state an extraordinary complexity in which all may be at work may be manifested. Thus, a progressive reaction in the connective tissue of the kidney may on the one hand cause degeneration of the essential secreting structures, and on the other may so affect the circulatory system as in the first instance to originate a functional hypertrophy of the heart, and then a premature senility of the organ, which in turn, by starving the peripheral vessels, may cause an increased transudation of lymph, with a consequent failure of oxygenation and death.

## CHAPTER II

# PATHOLOGY OF THE BLOOD

By A. E. BOYCOTT

THE great function which blood discharges as the medium of exchange between the outside world and the body, and between one part of the body and another, is intimately bound up with the fact that it circulates. In considering the pathology of the blood, it is, however, essential to look upon the blood, together with certain parts of the bone marrow, etc., as primarily constituting an organ whose chief business it is to maintain its own individuality. We recognize the individuality of a cell, a tissue or an animal by the presence of specific structure and specific composition, and by the tendency to resist any alteration in such structure and composition, and to correct as far as may be any alterations which may be brought about. The blood exhibits these characters particularly clearly. Its anatomical structure and chemical composition are specific, characteristic, and remarkably constant throughout all vertebrates, and to some extent all metazoa, and they differ widely from those of any other tissue. There is, for example, much less difference between the bloods of man and the lobster than there is between human blood and human muscle. Since the blood is, in fact, the medium whereby foodstuffs, excreta and the like are carried about the body, its composition can never be exactly alike at any two places or at different times; the variations due to this cause are, however, so small that the majority of them cannot be actually demonstrated, and they are always overshadowed by the prevailing and essential uniformity.

**The Total Volume of the Blood.**—In man the blood constitutes about 5 per cent. of the total body weight, in rabbits about 5 per cent., in dogs 7 or 8 per cent., in rats 6½ per cent., in guinea-pigs 4 per cent., and in mice 6 per cent. Young animals tend to have relatively rather more blood than old individuals of the same species. Under most circumstances the volume is kept almost constant, and it is difficult to produce any material, and especially any lasting, alteration in the volume by experimental procedures.

If one, for example, seeks to increase the volume of the circulating blood by the injection of salt solution, most of the added liquid is

soon passed out of the vessels, partly by the urine and alimentary canal, partly into the tissues. This takes place very rapidly, even when the kidneys are excluded by ligation of the vessels. Thus, in dogs into whose veins is injected a volume of salt solution equal to half the volume of the blood, one-third to one-half of the injected liquid is found to have already left the bloodvessels during the ten or fifteen minutes occupied by the injection; most of the rest soon follows, though a long time may elapse before the original volume is quite restored. The result is essentially the same whether hypotonic (0·3 per cent.), isotonic (0·8 per cent.), or hypertonic (2·0 per cent.) salt solution is injected.* The same readjustment of the blood-volume is found if the liquid injected into the vessels is the animal's own tissue fluid. This can be effected by injecting a large amount of concentrated solution of dextrose intravenously: the volume of the blood is at first much increased by fluid being dragged in from the tissues, but the great bulk of this is, along with the sugar, very soon passed out of the circulation again. Such solutions are, of course, useless for respiratory purposes, and only hamper the intake of oxygen by diluting the concentration of hæmoglobin per unit volume of blood. This is, however, evidently not the reason why they are turned out of the blood; for just the same result is obtained if for salt solution we substitute the fresh blood of another animal of the same species. Transfusion of blood in this way is immediately followed by a rise in the concentration of hæmoglobin in the blood of the recipient, and after a few hours it is found that the volume of the blood is again reduced to the normal level. Be it noted that this involves the ejection from the circulation, not only of the injected plasma, but also of a volume of the animal's own plasma equal in bulk to the injected red corpuscles; these remain inside the vessels. More striking still, perhaps, is the experiment in which the animal is transfused with its own normal blood ("plethora apocoptica"). This can be done by driving all the blood out of, *e.g.*, the legs by firm centripetal bandaging. As a result, it is found that the specific gravity of the blood rises, while that of the extravascular tissues falls, indicating that fluid has passed from the blood to the tissues, and showing the activity of the mechanism whereby the volume of the blood is kept adjusted to the level appropriate to the capacity of the vessels.

If, on the other hand, one essays to diminish the volume of the blood, similar difficulties are met with. The obvious experiment here is to withdraw blood from the circulation. This is immediately followed by the intaking of a corresponding bulk of liquid from the tissues. So rapidly does this occur that, in an animal bled to death from a divided carotid artery, the last portions of blood obtained may be definitely less concentrated than the first. If the hæmorrhage is prolonged over so short a period as a quarter of an hour, the differ-

* Leathes, *Journ. of Phys.*, vol. xix., p. 1.

ence between the first and last portions is usually obvious. This rapid dilution of the blood during and after hæmorrhage is the explanation of the apparently remarkable phenomenon that a person with 3 or 4 litres of blood may within a few hours lose by hæmorrhage a bulk of blood found by measurement to be perhaps twice as great.

The restoration of the volume of the blood after hæmorrhage can only occur if a sufficient bulk of fluid can be spared from the extravascular tissues. In animals deprived of water it takes place more slowly than in those allowed to drink freely. Considerable variations are also found both among different individuals and between different species of animals. Rabbits, for example, generally restore the original volume of the blood within two or three hours after being bled to a third or a half of their total hæmoglobin. Dogs may do so; more commonly, however, the concentration of hæmoglobin in their blood continues to fall progressively for some time after a severe hæmorrhage, and the full restoration of volume may not be complete for several days. Much the same generally occurs in man. Now, in dogs exact experiment has shown that the volume is not restored much, if at all, sooner if, immediately after the hæmorrhage, the blood removed is replaced by injecting an equal volume of salt solution into the veins. The salt solution is treated as an essentially foreign substance, and consequently ejected. There is, on the other hand, evidence to show that the restoration of volume in the dog is materially accelerated, and may, in fact, be as quick as in the well-watered rabbit, by placing a quantity of water in the stomach instead of directly into the circulation. This presumably affords a reservoir whence may be put together a plasma sufficiently normal to satisfy the economy. It has long been recognized in man that the immediate effects of a severe hæmorrhage on the respiratory, cardiac and other functions may often be corrected by adding water to the body, either by direct intravenous injection or by introducing it under the skin or into the bowel. The results of experiment indicate that the latter methods are probably preferable, since the volume is then made up with plasma rather than with artificial solutions, and it is significant that the practice of direct intravenous injection has now to a considerable extent been replaced by the other methods.

These considerations have some bearing on the question of the mechanism whereby the adjustment of the volume of the blood is effected. Considering that any increase of volume by addition of liquid is soon corrected, no matter what the nature of the injected fluid, and that the rate at which the excess leaves the vessels is very quick at first, and becomes slower and slower as the composition of the blood is reduced more nearly to the normal, one is led to suppose that the restoration of volume is due to the disturbed correlation between the volume of blood and the natural capacity of the vas-

cular system. It is certain that the injection of considerable quantities of liquid into the circulation has no material lasting effect on arterial pressure. But there are grounds for believing that under these circumstances some rise of venous pressure, and hence some increase of capillary pressure, is brought about. This may be the immediate cause of fluid being expelled from the vessels. A considerable hæmorrhage in the same way does not necessarily cause any but a transitory fall in arterial pressure. The vessels are, however, underfull, and the alteration of the relation between intravascular and extravascular tissue pressures may well result in fluid being sucked into the circulation. The experiments on bleeding and infusion already noted show, however, that these factors are not in all cases paramount, but may be overridden by considerations of the nature of the fluid available for the restoration of the volume.

Alterations in the natural capacity of the vascular system bring about corresponding changes in the blood-volume. If the capacity is diminished, as in "plethora apocoptica," the volume is diminished. This can also be brought about by a general rise in arterial pressure (*e.g.*, adrenalin). If the capacity is increased and the blood-pressure falls (*e.g.*, section of the cord, shock), the concentration of the blood is diminished and the volume increased.

It is evident, then, that the tissues of the body co-operate in seeing that the blood should be just the right volume to fill the vascular system to which it belongs. No doubt the heart and vessels work most economically if this condition is fulfilled. Otherwise it would appear to be better after a hæmorrhage to leave the volume of the blood less than normal, and so keep up the concentration of hæmoglobin. In this way the right amount of hæmoglobin could be sent through the lungs and round the body every minute without it being necessary for the heart to pump a larger quantity, which it has to do if the volume is restored and the hæmoglobin concentration consequently diminished. We may surmise that, if the volume of blood is much less than normal, the heart's intake on the venous side cannot be properly effected. On the other hand, less trouble is made about the volume being too large. After the injection of salt solution or the animal's own plasma, the hæmoglobin concentration is diminished, and there is no good reason why the total volume should not be brought back to normal. But after the injection of blood the hæmoglobin concentration is increased under these circumstances the volume may remain above the normal level to avoid the difficulty of excessive viscosity. In thinking, therefore, of the regulation of the volume of the blood, the relative importance of at least three factors must be considered—the relation to the volume of the vascular system, the concentration of the oxygen-carrying power and the viscosity, the normal of each one being that which fits best with the possibly conflicting interests of the other two. The capacity of the blood to carry other

things than oxygen has probably so wide a margin of safety that it may be neglected.

**Regeneration of Blood after Hæmorrhage.**—The restoration of the volume of the blood at the expense of the tissue fluids immediately after a hæmorrhage has been already dealt with. This tissue fluid is, however, more dilute than normal plasma. Observations on the specific gravity of the plasma after hæmorrhage show that there is at first a very rapid fall, which is soon replaced by a quick, though less precipitous, rise. In the rabbit the normal figure is approximately regained in a few hours, in man in a day or two. These experiments show that after the volume is restored (rabbit), or while it is being restored (man), the body sets to work and quickly adjusts the composition of the plasma as near to normal as may be. This rapid regeneration of plasma doubtless concerns in the main the inorganic constituents; the replacement of the specific proteins requires a longer time, though we have no very exact information on this point.

The regeneration of the hæmoglobin which has been lost is a more gradual process. Hæmoglobin loose in the circulation is useless to the higher animals, and is taken up by the tissues or excreted as a foreign substance; there are reasons for believing, indeed, that it may be actually poisonous. Its rate of regeneration, therefore, may be limited, not only by the time required for its manufacture, but by the possibilities of proliferation possessed by the cells in which it must be contained when set free in the circulating blood. The rate of regeneration can be accurately ascertained only by methods which determine the total amount of hæmoglobin in the body. Since, however, the total volume of the blood generally remains pretty steady, the concentration of hæmoglobin usually indicates fairly well the total quantity also. The restoration is an orderly process, directed towards and generally attaining, as in other true regenerations, a definite and desirable end. The stimulus to regeneration is the deficiency of red cells to carry oxygen.

In the rabbit a loss of about one-third to one-half of the total hæmoglobin is made good in about three weeks, about 2 per cent. of the total normal amount of hæmoglobin in the body,* and about 5 per cent. of the hæmoglobin lost, being restored daily. As far as our information goes—and it is at present meagre on this point—regeneration in healthy persons is proportionally slower. That the rate of regeneration becomes slower as the normal level is more nearly approached is by no means clear. Assuming—which may not be proper—that the stimulus is greatest when the defect is greatest, a constant rate of regeneration through-

* *I.e.*, in man about the amount of hæmoglobin contained in 60 c.c. of normal blood. For every kilo of body weight man has hæmoglobin having an oxygen capacity of about 9 c.c.; dogs, 15 c.c.; rabbits, 7 c.c.; rats, 10 c.c.; mice, 9 c.c.; and guinea-pigs, 6 c.c.

out may be taken to indicate that the regenerative mechanism is working to its full capacity all the time, and that the power of growth of this mechanism is the factor which limits the rate of regeneration. The capacity of the mechanism may, however, be much increased by longer and more intense stimulation. Repeated bleedings may more than double the rate, no doubt because they eventually lead to an hypertrophy of the regenerating apparatus.

In adult life red blood-corpuscles arise in the bone marrow, either exclusively or to such a preponderating extent that other organs may be neglected. In view, however, of the importance of the liver and other organs as sites of hæmopoiesis in fœtal life, the possibility of the extension of the area of growth in the adult under abnormal circumstances must not be altogether forgotten. As a rule in man there is no need for any such extension to transgress the anatomical limits of the bone marrow. Large parts of the marrow in normal adults are occupied by a tissue which is little more than fat; this is especially the case in the shafts of the long bones. The apparatus for making red cells may therefore be much hypertrophied within the limits of the bones themselves, and, in fact, it is found that under circumstances when a call is made for this hypertrophy a large part or the whole of what is usually fatty marrow may be replaced by a red tissue in which active proliferation of red cells is proceeding. The bulk of this tissue may be further increased by the enlargement of the medullary cavity in the bones.

It is clear from these considerations that, in our conception of the component parts of the tissue "blood," we must include the parts of the bone marrow which give rise to red cells, and also those in which leucocytes take origin. On the other hand, the whole of the anatomical marrow must not be included; the supporting framework, the fat, the bone-modelling apparatus, are clearly not part of the blood.

The rate of regeneration is therefore necessarily ultimately limited by the power of growth of the marrow. A sudden call for more red cells in the circulation leads to the extrusion from the marrow into the blood of immature forms of red cells.* These vary in immaturity from the large nucleated cells (megaloblasts), through the smaller nucleated cells (normoblasts) which are derived from them, to non-nucleated discs which show that they have been, as it were, put out in a hurry by their being too small or badly shaped, or by containing too little hæmoglobin or obvious remnants of nucleus (polychromasia, basophilia). In man megaloblasts or the corresponding non-nucleated form (megalocytes) do not commonly appear in the circulating blood during regeneration after hæmorrhage, though they may do so rather freely in smaller animals.

* Jones, *Journ. of Path.*, vol. xv., p. 9. For the histology in man see Emerson's *Clinical Diagnosis*, 2nd ed., 1909, and Armit's translation of Ehrlich and Lazarus's *Anæmia*, 1910.

The recognition of the other forms of immature red cells is, however, of importance as affording evidence of the activity of the regenerative process. They are not, however, to be regarded as in themselves reparative. Regeneration involves the formation of normal tissue, in the case of blood of normal red cells. The object of the premature extrusion of ill-made red cells is to tide over the deficiency of circulating hæmoglobin until enough normocytes can be made to take the place of those which have been lost. The immature forms may be less effective than normal cells, either by being bigger, and therefore having a relatively smaller surface for gaseous exchange, or by containing too little hæmoglobin. Red cells with nuclei or the remnants of nuclei have also the disadvantage that they themselves use up much more oxygen than normal erythrocytes.* The hæmoglobin in them, however, has a normal oxygen-carrying power.

Regeneration may be interfered with if the growth of the marrow is obstructed. Severe hæmorrhage may itself do this by limiting the supply of oxygen to the marrow cells; the poisons developed in infections may have the same effect. A deficiency of iron much retards regeneration, though it is doubtful whether this factor is ever of much importance in man. Regeneration is less active in the adult and aged than in young individuals.

Regeneration of red cells which have been lost as oxygen-carriers by being destroyed inside the body follows the same lines. There are reasons for thinking that the presence of the remains of the cells stimulates regeneration. Almost all the iron and much of the original hæmoglobin may be ready at hand in the body for the construction of new red cells. Experiments on animals show definitely that the iron-containing remnants of hæmoglobin which accumulate in the spleen are used up during regeneration. The question as to whether the mode of regeneration is altered as well as the rate is discussed below (p. 27).

**Destruction of Red Cells: Hæmolysis.**—During normal life destruction and regeneration of red cells is constantly going on. Why this should be so we do not know; it is convenient to say that red corpuscles ultimately wear out, and to attribute their destruction to a process of natural senescence. How much blood is thus changed every day is unknown, nor have we any idea of the natural length of life of a red cell. The constant activity of the marrow and the steady formation of bile pigment show, however, that there is a normal destruction. The effete red cells are probably not dissolved in the circulating blood, though the absence of hæmoglobin from the plasma and urine does not necessarily prove this. In animals about 1 per cent. of all the red cells in the circulation must be dissolved simultaneously before any hæmoglobin appears

* Douglas, *Journ. of Phys.*, 1910, vol. xxxix., p. 493.

in the urine. Free hæmoglobin is quickly removed from the plasma, even if none is excreted by the kidneys. In this way a good many red cells could be destroyed, a few at a time, without giving rise to obvious signs. It appears, however, that red cells which are to be destroyed are eaten by phagocytic cells, the cell disintegrated and the hæmoglobin decomposed in the interior of endothelial and other cells in the spleen, bone marrow, liver and lymphatic glands. The remains may be recognized for some time within the phagocytes as globules and fragments containing hæmoglobin; the fragments then begin to give the microchemical tests for inorganic iron, which indicate the disintegration of the hæmoglobin. The iron in great part remains *in situ* as "hæmosiderin" (an iron oxide protein compound), while the hæmatoporphyrin part is presumably excreted as bile pigment. By this process no risk is run that the valuable constituents of the cells will be excreted and lost to the body. The view that cells which are destined to shortly break up are taken out of the circulation by the phagocytes, probably with the idea of avoiding intravascular hæmolysis, is supported by the observation that, if considerable destruction of red cells within the circulation is induced by such agents as phenylhydrazine or hæmolytic serum (*infra*), extensive phagocytosis of apparently healthy red cells by endothelial cells may be found. The cells eaten are presumably not really healthy, but injured by the poison administered, and if left alone would shortly dissolve in the circulating blood.

Hæmolysis may be effected in a variety of ways—(1) *Physical:* If red cells are placed in distilled water, salts diffuse out and water is taken up until the cell bursts; conversely, they lose water and shrivel if they are placed in concentrated salt solutions. These observations show that a red cell has a differentiated outer layer or cuticle. With human blood hæmolysis takes place with solutions of sodium chloride of about 0·4 per cent. and less; all the cells are not equally resistant, and a few are not laked even in distilled water. Mechanical violence, such as shaking with shreds of asbestos or alternate freezing and thawing, also produces hæmolysis. (2) *Fat solvents* and substances which can combine with the cholesterol and "lecithin" of the red cells: ether, chloroform, bile salts, saponin and soaps. Some of these are intensely hæmolytic, and show that the structural integrity of red cells depends on its lipoids. (3) *Various chemical substances*, such as ammonium salts, arseniuretted hydrogen, aniline, dinitrobenzene, pyrogallic acid, etc. (4) *Poisons of biological origin*, produced by animals (*e.g.*, snakes, spiders, toads) or plants (*e.g.*, ricin from castor-oil seeds, phallin from toadstools), including bacteria (*e.g.*, tetanolysin from the tetanus bacillus). In some cases these probably act as general protoplasmic poisons, with a specific point of attack; others by lipoid combination. (5) *Serum hæmolysis.* The serum of one

species of animal is often hæmolytic towards the red cells of another species; guinea-pig serum, for example, usually dissolves ox red cells and dog serum rabbit cells. Rabbit serum, on the other hand, is not hæmolytic to human red cells, but soon acquires that property in a rabbit repeatedly inoculated with human cells. The mechanism of hæmolysis in these cases is dealt with elsewhere (p. 153).

Extensive intravascular hæmolysis seldom occurs in human pathology. Red cells are mechanically destroyed by endoglobular parasites (malaria); but, apart from rare cases of poisoning with some of the substances mentioned, the only conditions requiring notice are paroxysmal hæmoglobinuria, blackwater fever and pernicious anæmia. The hæmolysis in this last disease is probably intracellular; at any rate, not enough hæmoglobin is set free in the circulation at once to give rise to hæmoglobinæmia or hæmoglobinuria. Nothing is known of the mechanism of blackwater fever,* in which attacks of hæmoglobinuria occur in malarious persons. In *paroxysmal hæmoglobinuria*† we have a condition in which exposure to cold, either of the whole body or of an extremity, precipitates an attack of intravascular hæmolysis, which is generally of such a degree that free hæmoglobin is passed in the urine. Attacks sometimes appear to be without any exciting cause. The red cells themselves are not abnormally hæmolyzable; but the serum contains —using the terminology at present in vogue—a hæmolytic immune body which can only combine with the red cells at a low temperature. When the temperature is thereafter raised, either experimentally in the test-tube or by the cooled blood returning from the extremities to the viscera, complement comes into play, and hæmolysis results. In mild attacks there may be albuminuria instead of hæmoglobinuria, and this condition generally precedes the hæmoglobinuria in an ordinary attack. Up to a certain point, therefore, the hæmin moiety seems to be taken up by the liver. It is of interest that the attacks of hæmolysis in both blackwater fever and paroxysmal hæmoglobinuria are accompanied by severe general illness, in the former condition often fatal. Experimental hæmolysis frequently causes death within a few minutes or hours when only a trivial quantity of red cells has been destroyed. Hæmolytic immune serum and some saponins are known to be active general tissue poisons, apart from their hæmolytic action, but the same thing is seen after intravenous injection of distilled water. Why hæmolysis in the blood should be dangerous is not known, but the facts supply another reason for avoiding intravascular in favour of intracellular destruction of red cells.

The resistance of red cells *in vitro* to hæmolytic agents varies in different conditions. Thus, during active regeneration the newformed red cells, which are liable to be imperfectly made, are broken

* Barratt and Yorke, *Annals of Trop. Med.*, vol. iii., p. 1.
† Macalister, *Quart. Journ. of Med.*, vol. ii., p. 368.

up more easily than normal cells by all hæmolytic agents. In jaundice their resistance to hypotonic salt solution is increased, while to saponin it is diminished, since the lipoid constituents are already to some extent occupied by bile salts. Caution is required before such results obtained *in vitro* are transferred to *in vivo* phenomena. The hæmolytic action of saponin and soaps, for example, is prevented by cholesterol (or serum), and is greatly dependent on their concentration. Though saponin, sodium oleate and hæmolytic immune serum all produce hæmolysis readily enough in the living animal, their action is quantitatively different *in vivo* and *in vitro*.

**Transfusion of Blood.**—When for one reason or another the vascular system contains too little hæmoglobin, it is an obvious therapeutic procedure to inject blood from another individual into the circulation. This procedure is known as "transfusion," as distinct from the "infusion" of a dead preparation such as salt solution. To escape from the inconvenience of obtaining human blood for transfusion, it was customary at one time to substitute that of a bland and gentle animal, such as the lamb. The compatibility of ovine blood and the human organism was, however, found to be not altogether in correspondence with that of the characteristics of the animals in question, and the process was sometimes attended with untoward accidents and the death of the recipient. Transfusion therefore fell into ill-deserved disrepute before it was fully realized that the blood of one animal injected into the circulation of an individual of another species is always more or less poisonous, though the exact degree of toxicity varies a good deal with different combinations of animals. Whether the animal organism can distinguish between its own hæmoglobin and that of another species is uncertain, but there is no doubt that it recognizes soon enough the presence of foreign red corpuscles, and, by the ordinary rules governing the maintenance of the composition of the body, treats them as foreign bodies, and destroys them pretty quickly. Hæmoglobin free in the circulation is, if present in more than a trace, excreted at once, whether it be the animal's own or that of another species. The fluid transfused for therapeutic purposes must therefore be derived from another animal of the same species, and must be whole blood. Whether blood in which coagulation has been inhibited by the action of alkaline citrates is permissible is rather doubtful; experimentally it seems safe enough. But defibrinated blood should certainly be avoided, since serum is poisonous to the species, and indeed the individual, from which it has been derived.*

If transfusion be practised on a normal animal within these limitations, the volume of the blood is for a time increased. Plasma is

* Brodie, *Journ. of Phys.*, vol. xxvi., p. 48.

however, very soon passed out into the tissues and by the kidneys, quickly at first, and then more slowly as the volume of the blood approaches its original level. The result of this is that the concentration of red cells in the blood, and therefore its oxygen-carrying power per unit volume, is increased. This condition is not, however, maintained indefinitely. Sooner or later the injected red cells disappear, partly by a deliberate attempt at readjustment on the part of the recipient, and partly by the natural senescence of the cells. In this way a mass of red cells equal to about one-third of that already possessed by the recipient animal disappears in ten or fourteen days after transfusion. If the recipient is materially deficient in red cells at the time of the transfusion, the rate of destruction is diminished ; the organism, when it is short of its own cells, will tolerate and use the red cells that it actively destroys if it has no need of them. By repeated transfusion the apparatus may be trained and the rate of destruction become much quicker. Destruction is effected by phagocytosis.

**Polycythæmia : Polycythæmic Plethora.**—By "polycythæmia" we mean—the derivation of the word being wholly immaterial—a condition where there is too much hæmoglobin per unit volume of blood. It is always accompanied by an excess of red cells. By "plethora" is signified a state in which there is too much blood. The examples of polycythæmia which are known may be grouped as follows :

1. *Concentration Polycythæmia.*—This is produced by a diminution in the volume of the blood, brought about as a rule by excessive loss or very deficient intake of water, as in cholera, profuse diarrhœa, vomiting, or complete starvation. From what has been already said with regard to the tendency to keep the volume of the blood constant, it will be realized that any case in which a material concentration of the blood is brought about by these causes is to be looked upon as showing a very serious disturbance of the normal arrangements. Since the total amount of hæmoglobin in the blood is normal, this sort of polycythæmia differs widely from those which follow, in which there is a real increase of hæmoglobin.

2. *Polycythæmia following Transfusion.*—As already explained, after transfusion of blood the blood-volume is soon restored to normal, and the concentration of hæmoglobin raised in proportion to the amount injected. The polycythæmia thus produced is of short duration, and the excess of red cells is destroyed within a week or two. If the quantity transfused is relatively very large, some increase of blood-volume may persist for a time ; this plethora avoids an inconvenient increase in the viscosity of the blood.

3. *Compensatory Polycythæmia.*—The normal concentration of hæmoglobin in the blood is doubtless adjusted to fit the facts that the air contains 21 per cent. of oxygen, and that man's circulation rate and consumption of oxygen are what they are. Any defect

in the intake of oxygen from the air to the tissues may result in a compensatory polycythæmia. Being aware of the general objection to a diminished volume of blood, we should expect, therefore, such polycythæmia to be brought about by an increase in the total hæmoglobin in the body.

Exposure to low atmospheric pressure—in other words, to air deficient in oxygen—as at high altitudes, leads to a well-marked increase of hæmoglobin per unit volume of blood. The increase begins at once, and may then perhaps be in part caused by a diminution of the blood-volume; but it progressively goes on for some weeks, and is then undoubtedly due to an increase in the total hæmoglobin in the body. On returning to sea-level it soon disappears.

A similar polycythæmia may be induced by interfering with the oxygen-carrying power of the hæmoglobin. This may be done experimentally by keeping animals in an atmosphere containing an amount of coal gas sufficient to saturate about one-quarter of their hæmoglobin with carbon monoxide. Red cells are regenerated until the actual oxygen-carrying power of the blood is restored; since the blood contains at first the normal amount of hæmoglobin, this results in a polycythæmia. It has been suggested that in pathological conditions in man the oxygen-carrying power of the hæmoglobin may be abnormal. No example of this has, however, been found. On the contrary, direct experiment has shown that in polycythæmia and anæmia, as in health, the oxygen-carrying power of the blood is proportionate to its colour—*i.e.*, to the quantity of hæmoglobin which it contains.

The oxygen relations of the air and tissues may also be upset if the circulation is impeded, and an exaggerated degree of polycythæmia may be due to cardiac disease, especially congenital abnormalities, such as pulmonary stenosis, in which there has been ample time for compensation. This polycythæmia is due to an increase in total hæmoglobin; there may also be a considerable excess of blood, so that the condition is one of polycythæmic plethora.

| | Hæmoglobin per Cent. | Grammes of Hæmoglobin per Kilo of Body Weight. | C.C. of Blood per Kilo of Body Weight. |
|---|---|---|---|
| Normal average .. .. .. .. | 100 | *i* | 50 |
| Congenital cardiac disease .. .. | 180 | 33 | 131 |
| Splenomegalic polycythæmia .. .. | 148 | 20 | 97 |
| | 176 | 37 | 160 |

4. *Cryptogenetic Polycythæmia* (*Idiopathic Splenomegalic Polycythæmia*).*—In this interesting disease the hæmoglobin is increased

* Weber, *Quart. Journ. of Med.*, vol. ii., p. 85.

to 130 or 160 per cent. By the carbon monoxide method of determining the total oxygen capacity and total volume of the blood, it has been found that the blood-volume is also much increased, and that therefore the total hæmoglobin in the body is increased much more than is indicated by the reading of the hæmoglobinometer. The condition is, in fact, one of true plethora, so long supposed to be a myth. In an average case with a hæmoglobin reading of 140 per cent. and some 9,000,000 red cells per cubic millimetre, there may be 5 or 6 litres of blood; and in an extreme case an average-sized man may have 10 litres of blood and 2½ kilogrammes of hæmoglobin, instead of the normal of about 3 litres and 400 grammes. None of the possible causes of polycythæmia are present; the circulation is defective in advanced cases, but it is a secondary failure brought about by the increased viscosity of the blood. The condition can hardly be a response to excessive blood-destruction—of which there are no signs—since we cannot believe that the erythroblastic apparatus would make such a perverted effort at regeneration as to produce two or three times too much hæmoglobin. The oxygen-carrying power of the hæmoglobin is normal. We cannot suppose that, if the normal destruction of senescent red cells were to cease, normal regeneration would go on so far beyond what was required. There is no evidence that the tissues want more oxygen than usual. The overgrowth of red cells is, in short, meaningless, purposeless and continuous, and the condition is to be regarded as a benign tumour of red cells. The sequence of events is doubtless that the marrow produces too many red cells, and passes them on into the blood. When the blood contained twice its normal number of red cells it would become about solid. Hence the total volume of blood is increased in order that the circulation may be maintained at all. The point at which the difficulties of increased viscosity outweigh the objections to an increased volume seems to fall at a concentration of 140 or 150 per cent. of hæmoglobin. If this view of the condition is correct, direct evidence of increased activity in blood-formation should be obtainable. Such is the case. The circulating blood contains a few normoblasts in most cases, and red cells which are too small, misshapen or which have less than the normal content of hæmoglobin, so that the red cells are increased relatively more than the hæmoglobin. These abnormalities indicate excessive activity of the erythroblastic apparatus. This is confirmed by finding post mortem that the area of marrow occupied by red cell formation is much increased. The enlargement of the spleen is secondary to the polycythæmia. The functional difficulties of polycythæmia arise from the increased viscosity of the blood. This is in relation to both the number of red cells and the percentage of hæmoglobin, since hæmoglobin forms such a large proportion of the solid matter that cells deficient in hæmoglobin become thereby more mobile.

Normal blood has about five times the viscosity of distilled water at body temperature. The cases of polycythæmia described above show figures two to four times as great.

**Anæmic Plethora.**—The old idea that persons who ate red meat and drank red wine in large quantities thereby stimulated the formation of red hæmoglobin, and were plethoric in the sense that they had more blood than those who led more abstemious lives, can no longer be maintained. The blood in average normal persons no doubt varies in quantity about as much as do other organs, ranging in the great majority of individuals within 10 or 12 per cent. of the mean. We do not, indeed, know of any example of plethora where the concentration of hæmoglobin in the blood remains normal. Plethora in human pathology is associated either with polycythæmia or anæmia. And by anæmia we mean a condition in which the quantity of hæmoglobin per unit volume of blood is diminished.

*Chlorosis* is a common form of anæmia among young females, to which class it is almost entirely restricted. The fundamental changes in the blood are two in number : (1) the total volume of the plasma is much increased ; (2) each red cell has less than the normal amount of hæmoglobin, the "colour index," as it is called, being less than 1. The total amount of hæmoglobin in the blood is within normal limits, and the reduction in the quantity per unit volume is due to dilution of the blood.* The red cells per unit volume are not decreased so much as is the hæmoglobin ; hence the total number of red cells in the blood may be greater than normal.

| | Hæmoglobin per Cent. | Hæmoglobin, Grammes per Kilo of Body Weight. | Blood, C.C. per Kilo of Body Weight. | Red Cells, Millions per C.Mm. | Relative Number of Red Cells per Kilo. | Relative Amount of Hæmoglobin per Corpuscle. |
|---|---|---|---|---|---|---|
| Normal women .. | 90 | 6·7 | 50 | 4·5 | 100 | 1·00 |
| In chlorosis .. | 47 | 6·9 | 105 | 4·0 | 187 | 0·58 |
| | 38 | 6·7 | 128 | 3·4 | 193 | 0·56 |
| | 32 | 6·5 | 143 | 2·6 | 165 | 0·61 |
| | 40 | 5·7 | 73 | 4·3 | 140 | 0·46 |
| | 58 | 6·9 | 86 | 3·6 | 138 | 0·80 |

The red cells are, apart from their low content in hæmoglobin, normal ; they may appear to be a trifle larger than usual, but this is probably due to their flaccid consistency. The oxygen-carrying power of their hæmoglobin is normal. The specific gravity and, as far as has been investigated, the composition of the plasma are normal.

The primary error in chlorosis, then, cannot be defective formation

* Smith, *Trans. Path. Soc. Lond.*, vol. li., p. 315.

of excessive destruction of hæmoglobin. The formation of red cells is abnormal, in that too many are put out into the circulation and each has too little hæmoglobin, and on the whole the colour index becomes lower as the degree of anæmia becomes more intense. Uncomplicated chlorosis is rarely if ever fatal, so that we have no information from examination of the marrow which might throw light on the condition. It is, however, impossible to imagine how an error of blood-formation of this type could lead to dilution of the blood. The view that the plethora is the essential and primary abnormality requires an explanation of the low colour index. This is perhaps furnished by the suggestion that the exchange of oxygen is facilitated by dividing the hæmoglobin into smaller pieces. The fact that chlorosis may be established and disappear again within a few days is greatly in favour of the disease being a primary plethora. It has also been shown that its cure consists in a concentration of the blood, the total amount of hæmoglobin remaining the same, while the quantity per unit volume is increasing rapidly. Under these conditions the number of red cells per cubic millimetre may rise considerably above the normal level—a further indication that the low colour index is due to the plethora, and not *vice versa*.

In cases of average severity the organism as a whole does not suffer from any marked symptoms of deficiency of oxygen. Compensation is no doubt effected by circulating the dilute blood more quickly. In very severe cases, however, especially those of long duration, a further compensatory attempt is made by way of increasing the concentration of hæmoglobin by active blood-formation. The signs of this may be found in the circulating blood in the shape of nucleated red cells and red cells which are undersized and variable in shape, and show irregular staining reactions. These changes are, however, secondary, and do not constitute an essential part of the pathology of the disease.

With our present knowledge, it is useless to speculate as to the cause of this form of plethora.

The anæmia of *ankylostomiasis* is another example of anæmic plethora. *Ankylostoma* is a small nematode worm which lives in the small intestine; it fastens on to the mucous membrane, and feeds on the tissues of its host. In so doing it often penetrates bloodvessels; the blood may either be eaten by the worm or escape into the bowel through the punctures. From the worm may be made extracts which are hæmolytic and anticoagulating to human blood *in vitro*. It is, however, clear that this blood-destruction must be quite small in amount, and without any real connection with the intense anæmia which may arise. For the diminution of hæmoglobin per unit volume is almost entirely due to increase of plasma, and does not correspond to an actual deficiency of hæmoglobin in the whole blood, though there is a small loss, probably due to intestinal hæmorrhage.

| | Hæmoglobin per Cent. | Hæmoglobin, Grammes per Kilo of Body Weight. | Blood, C.C. per Kilo of Body Weight. |
|---|---|---|---|
| Normal .. .. .. | 100 | 6·7 | 50 |
| Ankylostomiasis .. .. | 44 | 5·2 | 86 |
| | 47 | 6·0 | 92 |
| | 41 | 5·5 | 98 |

As in chlorosis, the colour index is low, and becomes lower as the anæmia becomes more severe. In moderate cases there may be no signs of active regeneration of red cells, though with severe degrees of anæmia these are obvious enough. How *Ankylostoma* upsets the mechanism which regulates the blood-volume is not known.

In chlorosis and *Ankylostoma* anæmia the primary change is a plethora. A similar dilution of the blood may accompany a state which is primarily an anæmia, as after hæmorrhage and in pernicious anæmia, or conditions which originally have nothing to do with the blood, as in renal disease or circulatory failure. It is known also from animal experiments that severe general illness from bacterial infections may lead to a considerable increase of blood-volume and a corresponding fall in the concentration of hæmoglobin. Our knowledge on these points is, however, very scanty, and indicates chiefly that one must be cautious in assuming that a diminution in the percentage of hæmoglobin or in the number of red cells per cubic millimetre of blood indicates an actual deficiency in the total amount of hæmoglobin or red cells in the blood rather than an increase in the plasma.

**Anæmia.**—Anæmia means a diminution in the concentration of hæmoglobin in the blood. With the anæmias which are primarily plethoras and due to dilution we have already dealt; it remains to consider those in which the essential error may be presumed to be connected with the life of red corpuscles and to result in there being too little hæmoglobin in the whole blood. Our knowledge of the total amount of hæmoglobin is in many cases very deficient; it may be that some of the states in which we at present assume that a diminution in the concentration of hæmoglobin in the circulating blood indicates a real deficiency may eventually turn out to be due to an increase of plasma. It is certain that the diminution of concentration is often greater than the absolute defect, and that some dilution of the blood makes the degree of anæmia seem more severe than it really is.

The normal amount of hæmoglobin in the blood of an adult is about 6 to 7 grammes for every kilogramme of body weight, the amount of blood being about 50 c.c. per kilogramme. A fair-sized individual has therefore about 400 grammes of hæmoglobin and 3 to

3½ litres of blood. This level is maintained pretty accurately, and is the result of a balance which is struck between the blood-destruction and blood-regeneration which is constantly going on. A deficiency of hæmoglobin may arise, therefore, (1) when the rate of destruction is normal and the rate of regeneration too slow; (2) when destruction is excessive and greater than regeneration can cope with; (3) when destruction is excessive and regeneration also abnormally slow.

Anæmia from defective regeneration occurs in a variety of circumstances where the growth of red cells in the marrow is interfered with. A moderate anæmia of this type results from chronic underfeeding, and may accompany any disease with defective nutrition. In the condition known as "aplastic anæmia" the marrow stops making red cells or leucocytes, destruction of effete red cells continues, and hence the person is soon anæmic. Anatomically, young forms of red cells are not numerous in the circulating blood, and the bone marrow shows little or no activity. The body is commonly invaded by bacteria; whether this is the result of the cessation of marrow activity or its cause is not known. Similar anæmias result if the marrow is largely destroyed by secondary growths of malignant tumours arising elsewhere, or if the space in the medullary cavities of the bones which is normally at its disposal is much curtailed (as in osteosclerosis), or if the marrow itself has undergone fibroid or gelatinous degeneration or is occupied by the abnormal overgrowth of leucocytes which we call "leukæmia." Considering the easy way in which blood-cells are produced all about the body in embryonic life, it seems somewhat singular that in these cases no considerable extramedullary foci of marrow are laid down to compensate for the deficiency of blood-forming tissue in the usual places. In the case of malignant tumours and leukæmia the possibility of some excess of destruction of red cells cannot be altogether excluded, and it is quite possible that poisonous substances inhibit marrow growth. But osteosclerotic anæmia seems to be simply the result of lack of room in the bones. The failure to effect a compensatory regeneration is the more singular since bone marrow is sometimes laid down in areas of ossifying calcification (*e.g.*, in the aorta or suprarenal) in the adult, and in animals the spleen may often take on an erythroblastic as well as leucoblastic activity in conditions of severe anæmia.

It is obvious that, if excessive loss of red cells (hæmorrhage, hæmolysis, etc.) occurs in any of these cases, the condition will be much aggravated. The combination seldom occurs. In one important disease, however, blood-destruction and blood-regeneration are both highly abnormal, though the relationship between the two defects is an open question. In primary progressive *pernicious anæmia* there is considerably less hæmoglobin in the body than normal,* destruction of red cells is excessive and regeneration is

* Smith, *Trans. Path. Soc. Lond.*, vol. li., p. 324.

irregular. The total volume of the blood may be normal, or increased by as much as 100 per cent. Dilution occurs especially in severe cases, and may reduce the concentration of hæmoglobin a good deal more than corresponds to the actual deficiency. But an actual deficiency always exists, the reduction in some cases being as much as 75 per cent.

| | Hæmoglobin per Cent. | Hæmoglobin, Grammes per Kilo of Body Weight. | Blood, C.C per Kilo of Body Weight. | Red Cells, Millions per C.Mm. | Relative Number of Red Cells per Kilo. | Relative Amount of Hæmoglobin per Corpuscle. |
|---|---|---|---|---|---|---|
| Normal .. .. | 100 | 7·0 | 50 | 5·00 | 100 | 1·00 |
| Pernicious anæmia | 43 | 3·4 | 49 | 1·62 | 32 | 1·35 |
| | 32 | 3·0 | 76 | 1·10 | 33 | 1·45 |
| | 26 | 1·7 | 49 | 1·05 | 20 | 1·24 |
| | 17 | 2·5 | 106 | 0·625 | 26 | 1·33 |
| | 15 | 2·3 | 117 | 0·50 | 24 | 1·50 |

Blood-destruction is evidently excessive; during life the excretion of urobilin in the urine is often much greater than normal, and iron is found every now and then in considerable quantities. After death large deposits of iron may be recognized microchemically in the liver, spleen and kidneys by the tests for inorganic iron. Direct chemical analysis shows that the liver, on the average, contains about four times as much iron as usual, and the kidney as much as fifty times. The mechanism of the destruction is unknown; there is no evidence that there is any actual hæmolysis in the circulating blood.

The anatomical changes in the blood and marrow show clearly that regeneration of red cells is not following the same lines as in a condition of anæmia due to single or repeated hæmorrhage. After blood has been lost from the body altogether, many of the red cells which are at first put out into the circulation from the marrow are in varying degrees immature (p. 14); as a whole, each red cell contains distinctly less than the normal quantum of hæmoglobin, so that the colour index is less than 1 (0·6 to 0·4). In pernicious anæmia, on the other hand, the circulating blood contains many red cells which are too big (megalocytes) and contain too much hæmoglobin, so that on an average the colour index is more than 1 (1·0 to 1·5). There are also many red cells which are too small (microcytes), and usually a number of deformed and irregular shape (poikilocytes). In the marrow, instead of the proliferation of normoblasts which is found in anæmia from hæmorrhage, there is an overgrowth of megaloblasts, the generation of red cells which normally gives rise to normoblasts, and of which the megalocytes of the blood are the product. The whole marrow is very active, and often widens its

anatomical boundaries by absorbing bone, and so enlarging the medullary cavities in the long bones. The megalocyte (and occasionally the megaloblast) is the characteristic of the blood in pernicious anæmia, and its predominance shows that marrow activity is taking an abnormal course which reproduces the condition which prevails in embryonic life.

We have, then, on the one hand excessive blood-destruction, and on the other an active but abnormal and megalocytic regeneration. The question remains, Which phenomenon is indicative of the primary change which ultimately forms the basis of the disease? It is in the first place possible that the megalocytic regeneration is the result of the excessive hæmolysis. The reaction of the marrow to loss of blood by hæmorrhage might easily differ from that excited by destruction of red cells inside the body, since in the latter case the stromata and other remnants remain behind, and might constitute a stimulus of a special kind. Experiments on animals show that destruction of red cells inside the body (by ricin, phenylhydrazine, etc.) often leads to a megalocytic regeneration, and a colour index of more than 1; the significance of this fact is, however, much diminished by the observation that in similar animals severe hæmorrhage may excite the megaloblasts of the marrow, instead of dividing into normoblasts, to get rid of their nucleus altogether and appear in the blood as megalocytes. In man severe and long-continued hæmorrhage does not result in a predominance of megalocytes in the blood; it has been also ascertained that the absolute deficiency of hæmoglobin in some of these cases is as great as that which obtains in pernicious anæmia, so that the difference in the nature of the response cannot be due to a difference in the amount of hæmoglobin lost to the economy. In malaria blood-corpuscles are destroyed within the body, as they are in pernicious anæmia; in the great majority of cases, however, this does not lead to a megalocytic response, though the occurrence of severe anæmia with a high colour index has been noted in a few old-standing, severe cases of malarial infection. The view, therefore, that megalocytic regeneration is due either to the degree or the kind of blood-destruction which goes on in pernicious anæmia must be regarded as not proved.

The alternative idea is that the excessive destruction of red cells is due to some abnormality of the red cells which finds a morphological expression in the megalocytic nature of many of the cells in the circulating blood. On this view the primary error is the production by the marrow of abnormal red cells, which are not so stable and resistant as those generated by the normal process; hence there is excessive hæmolysis and more or less severe anæmia. The cause of the primary error of growth in the marrow is unknown. It may be due to poisons brought into the body from without; the inflammatory and atrophic changes which are found in the alimentary

canal may indicate the mode of entrance of such poisons, though they are equally explicable either as evidence of the site of origin of substances which cause hæmolysis directly or as being simply the result of severe anæmia. Or the mistake made by the marrow may be of the same kind as that made by any other tissue when it starts a malignant tumour; in this connection it is perhaps suggestive that megalocytic blood is a reversion to an embryonic type of growth, and that the disease is almost inevitably fatal. There are no grounds for thinking that the error is congenital; cases in children are very rare, and the commonly familial distribution of such affections is not seen in pernicious anæmia, though it is a well-marked feature of the relatively mild anæmia known as "acholuric jaundice," which appears to be due to excessive hæmolysis of red cells which are ill formed owing to an inborn defect in the marrow. The direct evidence in favour of this view of pernicious anæmia is therefore very scanty.

Apart from pernicious anæmia, conditions rarely occur in which the blood presents the same megalocytic character. It occasionally happens that a person suffering from malignant disease, malaria, severe sepsis, etc., shows changes in the blood and elsewhere which appear to be identical with those which are characteristic of the idiopathic disease. Pernicious anæmia is not rare, and it is not clear that such cases are not examples of pernicious anæmia associated with some other disease. This explanation will not, however, hold good in the cases where a severe anæmia with megalocytic red cells is due to the parasite *Bothriocephalus*. Only a small proportion of persons harbouring this tapeworm suffer from anæmia, but the etiological importance of the parasite is shown by the beneficial effects of its expulsion from the alimentary canal. Unfortunately, it is not known whether there is in *Bothriocephalus* anæmia a real deficiency of hæmoglobin, or only a diluted blood, and whether there is any excess of hæmolysis comparable to that of pernicious anæmia.

States of anæmia which are due primarily to excessive hæmolysis without any gross abnormality in regeneration are not known to be of very frequent occurrence. Blackwater fever and paroxysmal hæmoglobinuria have been already mentioned; in malaria a considerable quantity of red cells may be mechanically destroyed by the endoglobular growth of the parasites at each life cycle. The destruction of red cells by exogenous poisons such as aniline, dinitrobenzene, toluylenediamine, snake venoms and the like, occasionally causes an anæmia. It is important not to assume that anæmia is due to excessive hæmolysis unless some evidence is available that such hæmolysis actually occurs. The fact, therefore, that substances hæmolytic *in vitro* can be extracted from parasites such as streptococci, typhoid bacilli, tetanus bacilli, *Ankylostoma* or *Bothriocephalus*, should not be taken to show that hæmolysis occurs in the diseases caused by them. The action of many hæmo-

lytic substances is much less *in vivo* than *in vitro*; in other cases (*e.g.*, ankylostomiasis, typhoid fever) it is known that excessive hæmolysis does not occur.

**Leucocytes.**—Leucocytes differ from most other cells in the body in being loose, each cell having no attachment to any general stroma or to its neighbours, and in this way being capable of great mobility. Leucocytes form part of the tissue blood in that they develop for the most part in the bone marrow, and have their natural home in the circulating blood. But in any ordinary individual there are probably quite as many leucocytes in the tissues (excluding the marrow) as in the blood, and in this way they differ widely from the other elements of the blood.

The functions of leucocytes are intimately bound up with the processes of defence of the body against harmful influences, especially those arising in connection with the invasion of the body by parasites. Their activities in this respect are dealt with elsewhere (p. 167); we may only note here that they include both the production of chemical substances useful for protection, and the disposal of parasites, and foreign particles generally, by actual phagocytosis. Correspondingly, we find that they are specially abundant in the tissues about the alimentary canal and in the lungs, where extraneous and harmful matter is particularly liable to penetrate the surface of the body. Phagocytosis generally occurs outside the vessels; when it takes place in the blood, the leucocyte and its contents quickly disappear from the circulation, presumably by settling down on the capillary wall.

In extra-uterine life in man the blood contains five well-defined species of leucocytes—lymphocytes, large hyaline leucocytes, neutrophile leucocytes, eosinophile leucocytes and basophile leucocytes. Normally, in 1,000 leucocytes about 600 are neutrophile, 300 lymphocytes, 50 large hyaline, 25 eosinophile, and 5 basophile. Neutrophile cells are most actively amœboid, the others in less degrees, though even lymphocytes are capable of slight movements. As regards the phagocytosis of bacteria, neutrophile cells are again first, and eosinophile cells fairly active; large hyaline cells are, however, the chief leucocyte phagocytic towards other animal cells (protozoa, tissue cells). In every way, however, the phagocytic power of leucocytes is not more than that possessed by many endothelial cells. In the adult all the different kinds of leucocytes arise in the bone marrow. It is probable that lymphocytes also come from the lymphatic glands, and large hyaline leucocytes from endothelial cells. Under abnormal circumstances it appears that a certain number of neutrophile and eosinophile cells may come from foci of proliferation in the spleen and lymphatic glands, but the proportion of the total number which arise in this way is never very considerable. The ultimate precursor of both red corpuscles and leucocytes in the bone marrow is

the same; by growth and elaboration the various kinds become separated off, and after an early point in their differentiation are perfectly separate and distinct species which are not interchangeable.

The number of leucocytes in normal blood varies a good deal, but it may be taken that an average adult has between 5,000 and 10,000 per cubic millimetre of blood. The number may be much diminished (*leucopenia*) by prolonged fasting and in old age—in fasting, doubtless, because the body is to some extent saved from the access of harmful influences, and in other respects reduced to the low state of activity which prevails in the aged. In disease leucopenia occurs when the activity of the marrow is depressed (as in aplastic anæmia) or otherwise occupied (as in pernicious anæmia), or if there is very little marrow (as in osteosclerosis). Leucopenia is also a constant feature of the condition called "splenic anæmia," of the nature of which nothing is known. Experimentally high degrees of leucopenia may be produced by causing some reaction to take place in the blood-stream in which leucocytes are involved. Thus, injection of large quantities of bacteria intravenously may cause the complete disappearance from the blood of the species of leucocyte (neutrophile) whose business it is to take up the foreign organisms.

**Leucocytosis** is said to exist when any of the kinds of leucocytes in the blood is increased to more than about three times its normal number. This increase most commonly affects neutrophile cells; since these form about two-thirds of the leucocytes, it generally results that there is also a definite increase in the total number of leucocytes. Thus, normal blood with 8,000 leucocytes per cubic millimetre, 62 per cent. of which are neutrophile, contains about 5,000 neutrophile cells per cubic millimetre. If the number of neutrophile cells be doubled, their proportion is raised to 77 per cent., and the total number of leucocytes to 13,000 per cubic millimetre. On the other hand, a species of leucocyte which normally constitutes only a small proportion of all leucocytes may be much increased without making the total number of leucocytes obviously abnormal. Thus, the number of eosinophile cells (normally about 2 per cent.) per cubic millimetre may be multiplied by ten without bringing the total number of leucocytes above 10,000 per cubic millimetre. The processes at work in the two cases are essentially the same. Hence leucocytosis should not be defined in terms of the total number of all kinds of leucocytes. The increase of leucocytes in the blood is not commonly a response to any necessity for increased leucocytic action in that position, but represents the passage of leucocytes from their place of proliferation in the marrow to the place in the tissues where they are wanted. Thus, in an acute abscess, stimuli in the form of products of the causative pyogenic cocci on the one hand, and of the destruction of tissue cells on the other, pass by the blood-stream to the marrow, and excite

proliferation of the cell species (neutrophile leucocyte) which is required at the abscess. Examination of the marrow shows that the precursors (myelocytes) of these leucocytes are in active growth. The leucocytes so produced are passed out into the blood, and as they reach the focus of inflammation become adherent to the capillary wall and are attracted to emigrate into the tissues towards the abscess. So long as a leucocyte is travelling freely in the blood-stream, it is obvious that it cannot come under the directive force of chemotactic influences; these can only be felt when the cell has come to rest, and can polarize itself towards the point of maximum concentration of the chemotactic substance. Since, therefore, the leucocytes are wanted at one particular point, and it is a matter of chance into which part of the body they may be carried, it is a clear advantage to have a large excess actually in the blood-stream at any one time. It must, however, be remembered that this is not always perceptible. There may be an active proliferation of leucocytes in the marrow, and an accumulation of these at some distant point of inflammatory activity, without their number in the blood exceeding the normal limits. The process at work in the body may differ only in degree, and not in kind, giving a leucocytosis in one case and none in another. These considerations do not apply to cases where leucocytosis is caused by generalized infections or by the absorption of toxic substances from, *e.g.*, the alimentary canal; we may suppose here that, in the absence of any localized focus, leucocytes are wanted all over the body as well as in the blood itself.

Each stimulus which excites the growth of leucocytes in the marrow is a specific stimulus to one species of marrow cell. Hence the excess of leucocytes in the circulating blood is composed in the main of one sort of leucocyte, the relatively negligible increase in other sorts being probably due to the mechanical effect of the hyperæmia of the marrow which doubtless accompanies its increased activity. In considering, therefore, the causes of leucocytosis, it is necessary to distinguish the kind of leucocyte involved.

1. *Neutrophile leucocytoses* occur in response to infections with many bacteria, of which the pyogenic organisms are the most important; thus, pneumonia, erysipelas, osteomyelitis, glanders, plague and any abscess generally cause a considerable neutrophile leucocytosis. All bacterial infections do not, however, produce this effect; in typhoid fever and tuberculosis the process excites the proliferation of endothelial cells, not of leucocytes, and no leucocytosis is aroused in Malta fever. Dead tissues and their autolytic products also stimulate neutrophile cells, and sometimes to such a degree as to cause a definite leucocytosis; this may be seen, for example, after the escape of blood into the peritoneal cavity or into the tissues, where the blood dies and becomes relatively a foreign body. The local accumulation of neutrophile cells

## LEUCOCYTES IN BLOOD IN HEALTH AND VARIOUS DISEASES.

| | Normal. | | Pneumonia. | | Abscess. | | Whooping-Cough. | | Ankylostoma. | | Trichina. | | Malaria. | | Syphilis. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Per 100 Leucocytes. | Per C.Mm. of Blood. | Per 100 Leucocytes. | Per C.Mm. of Blood. | Per 100 Leucocytes. | Per C.Mm. of Blood. | Per 100 Leucocytes. | Per C.Mm. of Blood. | Per 100 Leucocytes. | Per C.Mm. of Blood. | Per 100 Leucocytes. | Per C.Mm. of Blood. | Per 100 Leucocytes. | Per C.Mm. of Blood. | Per 100 Leucocytes. | Per C.Mm. of Blood. |
| Lymphocytes .. | 33 | 2,600 | 11 | 2,900 | 8 | 1,500 | 62 | 21,100 | 7 | 3,100 | 20 | 2,100 | 12 | 700 | 34 | 4,400 |
| Large hyaline .. | 4 | 300 | 1 | 300 | 2 | 400 | 1 | 300 | 1 | 440 | 5 | 500 | 32 | 1,900 | 20 | 2,600 |
| Neutrophile .. | 60 | 4,800 | 87 | 22,600 | 89 | 17,000 | 34 | 11,600 | 19 | 8,400 | 41 | 4,200 | 54 | 3,200 | 41 | 5,300 |
| Eosinophile .. | 2 | 200 | 1 | 300 | 1 | 200 | 2 | 700 | 73 | 32,100 | 34 | 3,500 | 1 | 100 | 4 | 500 |
| Basophile .. | 1 | 100 | — | — | — | — | 1 | 300 | — | — | — | — | 1 | 100 | 1 | 100 |
| Total .. .. | — | 8,000 | — | 26,000 | — | 19,000 | — | 34,000 | — | 44,000 | — | 10,000 | — | 6,000 | — | 13,000 |

round dead tissue, as in an infarct or a sterile surgical incision, is generally more perceptible than the increase in the blood. In the same way malignant tumours cause a local, and often also a general, neutrophile response.

2. ***Lymphocyte leucocytosis*** is ill understood. Lymphocytes are proportionately rather more abundant in children than in adults, and a leucocytosis in which the increase is wholly or chiefly constituted by these cells occurs in a variety of infective conditions in children. It is particularly well marked in whooping-cough, though not constant, and there is no known infection to which a lymphocyte leucocytosis is the regular response. In the aged it sometimes replaces a neutrophile leucocytosis (*e.g.*, in pneumonia). The relative increase in lymphocytes produced by a paucity of neutrophile cells should not be mistaken for a lymphocytosis.

3. ***Eosinophile leucocytosis*** occurs in some cases of asthma, a local accumulation in the lungs and walls of the bronchi being much more frequent than an excess in the circulation; also sometimes in association with the bullous skin eruptions, such as dermatitis herpetiformis. A considerable eosinophile leucocytosis occurs also in response to the presence of some worms in the intestine (*Ankylostoma, Ascaris*), in the blood (*Bilharzia*) or in the tissues (*Trichina*). Examination of the bone marrow shows a proliferation of eosinophile myelocytes, just as the neutrophile myelocytes are predominant with a neutrophile leucocytosis; with *Trichina* there is also a local accumulation of cells round the parasite, constituting an eosinophile abscess parallel to the neutrophile abscess caused by pyogenic cocci.

4. ***Large hyaline leucocytosis*** is a response to infection by protozoa, as in syphilis, malaria and trypanosomiasis. The fact that smallpox is accompanied by a similar change is evidence of some weight that the causative organism is protozoal rather than bacterial.

5. ***Basophile leucocytosis*** is unknown.

Such are the general principles which underlie the occurrence of leucocytoses. Their complete and specific development may, however, be interfered with in many ways. Thus, in acute lobar pneumonia the reactive power of the marrow may be depressed by the poisons of the pneumococcus; and though there is a large accumulation of neutrophile cells in the lung, there may be no leucocytosis. In the same way, the deficient supply of oxygen to the marrow caused by the anæmia of ankylostomiasis may prevent the due development of the usual excess of eosinophile cells in the blood. In many cases mixed infections complicate the result: in smallpox, for example, when the bullæ in the epidermis become infected with pyogenic organisms, the large hyaline leucocytosis which is characteristic of the disease is replaced or obscured by a neutrophile leucocytosis. Mixed infections illustrate well the specificity of the leucocytic response; thus, if an abscess is produced by staphylococci

in a person in whose blood the eosinophile cell preponderates because he has trichinosis, the pus contains neutrophile cells alone.

**Destruction of Leucocytes.**—During ordinary life leucocytes are constantly being destroyed, and, as with red cells, a fresh supply is constantly coming from the bone marrow. In variable but always considerable numbers, they leave the body altogether by crawling out through the free surfaces—the alimentary canal, the respiratory passages, and to a less extent the urinary tract. From analogies in the lower animals, it is suggested that the leucocytes which do this are those which have taken into their bodies bacteria and other foreign particles, and adopt this unselfish manner of putting these outside the body. Direct demonstration that this is the case in the higher mammals is difficult to obtain. Examination of the walls and contents of the bronchi and bowels show that the number which emigrate to the outside world in these situations is very large, while in the urinary tract it is comparatively negligible. It is suggestive that it is in the two former situations that an abundant stream of foreign bodies of one kind and another is constantly being presented, and to some extent is gaining entrance, to the body, while the inside of the urinary apparatus is commonly sterile and innocuous.

Leucocytes which take up foreign bodies, whether these come into the body from without or arise by tissue disintegration from within, do not always leave the body. They may wander off into the tissues or the lymphatic glands or spleen, and perish there. It often happens that they are themselves eaten by the cells of malignant tumours and by endothelial and other normal tissue cells. This attitude on the part of tumour cells is consistent with their generally lawless behaviour, but one can only account for the unnatural cannibalism which is often seen in, for example, the giant cells of bone marrow by supposing that the leucocytes they eat have become obnoxious to the economy, presumably by taking up objectionable substances.

When active inflammatory processes arise in the body, the destruction of leucocytes may be enormous. The whole circulating blood normally contains enough leucocytes to make about 10 or 20 c.c. of average pus. A moderate suppuration may therefore produce daily a quantity of pus which contains more dead leucocytes than are naturally present in the whole blood. Thus an acute lobar pneumonia involving half of one lung entails the destruction of vast numbers of leucocytes. As has been already noted, regeneration is abundant, and examination of the bone marrow in such cases shows an overgrowth of leucoblastic tissue.

These phenomena concern chiefly the neutrophile leucocytes, since they are the most phagocytic and are specially involved in bacterial infections (which are most frequent in mammals). They apply, however, to the other sorts as well.

**Leukæmia.**—Leukæmia is a condition in which, along with a more or less severe anæmia, there is a large increase in the leucocytes, which number in an average well-developed case about quarter to half a million in a cubic millimetre of blood. It occurs in two forms. These do not represent processes of essentially different kinds, but the obvious characteristics are sufficiently distinct to warrant their separation.

In *myeloid leukæmia* all the species of leucocyte are much increased. The blood also contains a great number (20 or 40 per cent. of all the white cells) of young forms. These may be either the immediate precursors of the neutrophile, eosinophile and basophile leucocytes which have reached that stage of differentiation in which the cytoplasm already contains the specific granulation (granular myelocytes), or the more remote stages of the same species of cells in which the granulations have not yet become distinct (non-granular myelocytes, premyelocytes, myeloblasts). Commonly all gradations can be traced between non-granular myelocytes through granular myelocytes to fully differentiated leucocytes.

In *lymphatic leukæmia* the increase is due to cells belonging to the non-granular type of leucocyte, which constitute anything up to 99 per cent. of all leucocytes present. In some cases the cells present are indistinguishable from the lymphocyte of normal blood. In others they resemble very closely the non-granular cells which are the precursors of the granular myelocytes. That they actually are of this nature is supported by the fact that some of them, and in some instances all of them, show distinct suggestions of a neutrophile or eosinophile granulation in the cytoplasm. In yet other instances the white cells are of forms intermediate between these non-granular myelocytes and lymphocytes.

Leukæmia is generally accompanied by anæmia, presumably because the marrow is mostly taken up with producing an excess of white cells. In myeloid leukæmia there are usually a great many nucleated red cells, mostly normoblasts, in the circulating blood. Since this may occur without a severe degree of anæmia, it possibly represents on the erythroblastic side the same activity that is causing the leucoblastic apparatus to put out myelocytes instead of fully-developed leucocytes. In lymphatic leukæmia these nucleated red cells are much less abundant, and may be singularly few when the anæmia is profound. It has been suggested that some of the lymphocyte-like cells in the blood are really erythroblasts in the stage before any hæmoglobin is developed in the cytoplasm.

Granular myelocytes may appear in the circulating blood in small numbers in any condition where the corresponding leucocytes are being produced in large numbers by the marrow. Thus neutrophile myelocytes occur fairly frequently, though never abundantly,

in many acute infections. It is, however, fairly clear that myeloid leukæmia is not a response to any stimulus of the same kind as is given by, *e.g.*, staphylococci to the growth of neutrophile leucocytes. Such an idea is contrary to what is known as to the specificity of the response by each cell species of leucocyte to each definite stimulus. In myeloid leukæmia there is a general overgrowth involving neutrophile, eosinophile and basophile cells. The cells are immature in type, and, if their powers of phagocytosis may be taken as an index, less efficient in the defence of the body against infection. In lymphatic leukæmia, whatever the exact type of cell present may be, all the cells are pretty much alike, as they are in a leucocytosis; but there is no parallel for an infection producing an outpouring of the very elementary non-granular myelocyte which prevails in many instances.

Leukæmia, indeed, represents a sarcoma of the leucoblastic, possibly also of the erythroblastic, part of the bone marrow. The different forms correspond to the different stages in the development of leucocytes. Just as in sarcomata of white fibrous tissue there are round-celled tumours, which correspond to the condition of a connective-tissue cell immediately after division, and tumours with spindle cells, corresponding to a half-grown fibroblast, as well as all the intermediate stages, so from the bone marrow there arise tumours of granular myelocytes, of non-granular myelocytes and of the still less differentiated forms. The white cells in the blood in leukæmia, especially the myelocytic forms, can start fresh foci of growth in other parts of the body away from the marrow, and the disease is as inevitably fatal as a typically malignant tumour growing from other tissues.

All "myeloid" and some "lymphatic" leukæmias take origin in bone marrow. It is possible that this is true also of the cases of lymphatic leukæmia in which the cells very closely resemble lymphocytes. It appears, however, likely that some at least of these arise in lymphatic glands. There seems to be a complete series of transitions from a lymphosarcoma arising in lymphatic glands without any change in the blood, and with destructive secondary growths, through a lymphosarcoma (lymphoma) with infiltrative deposits, which may show a normal or a leukæmic blood, to a definite lymphatic leukæmia of the lymphocyte type in which it is not obvious whether the involvement of lymphatic glands is primary or secondary. In chloroma multiple tumours of lymphoid cells are associated with a leukæmia of non-granular myelocytes. This separation of lymphocytic leukæmias is supported by the fact that they do not change into a myeloid type during the progress of any individual case. On the other hand, the transition from a preponderance of granular myelocytes to a stage where only their non-granular precursors are present is not infrequent in the course of a case of myeloid leukæmia.

Other tumours of bone marrow are known. Thus, multiple myelomata may be composed of granular myelocytes, non-granular myelocytes or of cells resembling plasma cells. There is a solid tumour of erythroblasts (erythrocytoma), and splenomegalic polycythæmia represents an adenoma of red cells. The relatively benign single myeloma and endosteal sarcomata arise in the bone marrow, but not from blood-forming tissue.

**Coagulation of the Blood.**—The clotting of blood withdrawn from the body is due to the conversion of the soluble fibrinogen into insoluble fibrin by the action of fibrin ferment. As to the origin of fibrin ferment we have at present no settled knowledge, but as a working hypothesis we may assume that a zymogen (prothrombin) exists in blood which, with the co-operation of calcium salts and another ferment (thrombokinase), becomes active fibrin ferment (thrombin). Blood does not clot during life, because there is no available thrombokinase. The origin of this ferment is not known, but it probably arises in shed blood from the leucocytes or possibly the blood-platelets. Thrombokinase, or something very like it occurs in many animal tissues besides the blood—in muscle, testis, liver, the substance of vessel walls, etc. It must not, however, be assumed that all ferment-like substances which are active in promoting the conversion of fibrinogen to fibrin are identical in their nature, origin and mode of action.

**Extravascular Coagulation.**—The rapid occurrence of clotting when blood escapes through a hole in the vessel wall is of some practical importance. When, for example, a small artery is divided, the muscular coat is stimulated by the injury and contracts, and the damaged cells in the wall of the vessel and the surrounding tissues furnish a supply of thrombokinase. In this way the bleeding very soon stops of itself if the blood is normal. The effective mass of clot which plugs the vessel is mostly composed of red cells entangled in the fibrin. If the blood is relatively poor in corpuscles, the plug will obviously be less firm, and hence the natural arrest of hæmorrhage is not so effective in conditions of anæmia. That the formation of a good clot is as important as the contractility of the vessel wall is shown in the condition known as *hæmophilia*. In this remarkable disease trifling cuts may bleed for days, leading to serious, and even fatal, deficiency in hæmoglobin. The condition is markedly hereditary. The great majority of cases occur in males, though transmission is through the females. The continuance of bleeding is obviously due to the absence or imperfect formation of clot at the site of injury to the vessel wall. Blood drawn from a hæmophilic at a time when there has not lately been any considerable hæmorrhage takes much longer than normal blood to clot outside the body—*e.g.*, an hour instead of ten minutes. Hæmorrhage, especially if often repeated, increases the rate of coagulation.

Hence, samples of blood taken from " bleeders " who have recently been bleeding may show a normal coagulation time. Inquiry has shown that hæmophilic blood is normal as regards the quantities of fibrinogen, calcium, prothrombin and thrombokinase. It appears, however, that the error lies in an unduly slow combination of calcium, prothrombin and thrombokinase to form fibrin ferment. Once the fibrin ferment is formed, coagulation occurs quickly enough. Clotting is also very slow when the vessel wall is so injured (as in ordinary bruising) that the hæmorrhage occurs into the tissues or into a cavity, such as a joint. As a result, the red cells may settle to the bottom of the effused blood before it clots, and ultimately a considerable quantity of clear serum may be found. This has given rise to an impression that some of the effusions in hæmophilics consist chiefly of plasma—that is, that the plasma leaks through holes which are not big enough to let out red cells. There do not seem, however, to be sufficient reasons for thinking that in true hæmophilia the liquid which escapes from the vessels is other than whole blood.

In rare cases the hæmophilic tendency is restricted to certain parts of the body—*e.g.*, to the head and neck. This condition is obviously susceptible of only one explanation—*i.e.*, that the slow clotting is due to a deficiency of thrombokinase in the vessel wall and adjacent tissues, and appears to be quite different from true hæmophilia.

Blood effused into the tissues or serous sacs may clot quickly, as it would do outside the body. Clotting is favoured by extensive injury to the tissues, whereby much thrombokinase is liberated. On the other hand, such collections of blood may clot on the outside and remain fluid within, owing to the absence of exposure to air, contact with foreign substances such as hair, and other conditions which favour the development of thrombokinase from the blood itself in ordinary external hæmorrhage. Large blood-clots within the body are sometimes liquefied in the centre by autodigestion.

**Intravascular Coagulation (Thrombosis).**—Clotting of blood inside the vessels of the living body occurs in a variety of conditions. As distinguished from extravascular and post-mortem clotting, the process is called *thrombosis* and the clot a *thrombus*. Structurally, most thrombi differ from ordinary blood-clot in that they consist chiefly of fibrin and leucocytes, the proportion of red cells being much less than in whole blood.

We may take as an example the case where thrombosis of a large vein occurs in consequence of a local injury to the endothelial lining. The first change appears to be a local accumulation of particles resembling blood-platelets at the point of injury, though there are obvious difficulties in the way of being sure by actual observation that this is always the case, and the statement is made without prejudice to the question whether blood-platelets are really pre-

existing elements of the blood with any substantial claim to morphological individuality. Leucocytes are soon added to the mass, and fibrin then becomes recognizable. By the further accumulation of leucocytes and separation of fibrin the thrombus quickly grows, and within a few hours a comparatively large vein may be in this way completely occluded. Such a thrombus is not altogether homogeneous in structure. It is commonly more or less laminated, indicating that its formation has not proceeded uniformly, but in stages. The distribution of leucocytes is often very uneven, some layers containing many, while in other places the fibrin contains none. This irregularity is due in part to the irregular formation, and in part to the subsequent movements of the leucocytes, many of which have doubtless invaded the clot subsequent to its formation. The quantity of red cells also varies in different places. Most of the clot contains none or hardly any, while in other places its substance is chiefly composed of them. The more rapid the process, the more red cells will be entangled. When the thrombus has become sufficiently big relatively to the lumen of the vessel to materially obstruct the circulation, some stagnation of blood is liable to occur, and there is a greater tendency for red cells to be included, just as it is necessary to keep the red cells moving rapidly past the accumulating fibrin if one wants to get a clean clot by the ordinary process of whipping blood. Between a completely occluding thrombus and the next branches of the vessel the blood may be at a standstill, as also in the clefts and cracks which are subsequently formed by the contraction of the fibrin. The blood in such areas forms a red clot similar to those which develop post mortem, and in this way the thrombus may be in parts opaque and red instead of translucent and grey. The minute structure of the fibrin also varies in different parts. For the most part in fairly typical threads, it sometimes occurs as thick ropes or as amorphous masses with a granular appearance.

The subsequent history of such a thrombus varies in different cases. If it is infected with micro-organisms, it may putrefy or be softened by the digestive ferments of the bacteria. From such thrombi pieces are readily detached and form emboli, as detailed later (p. 303). Large thrombi, and especially thrombi which, as may happen in the auricles, have become detached from the wall on which they originally formed, may become fluidified in the centre by autolysis. Of more interest is the fate of the aseptic thrombus which does not lose its original firm consistence, and remains *in situ*. The presence of this mass of dead matter excites an inflammatory reaction. Leucocytes invade it, and the connective tissue of the vessel wall very soon shows evidence of active growth. Along with new-formed capillaries from the vasa vasorum, the proliferating white fibrous tissue grows into the thrombus, and by the ordinary process of organization converts it into a piece of live tissue. Some

of the abundant capillaries may make connections with the pervious parts of the vessel on either side of the obstruction, and by their anastomoses restore a path by which blood may once more pass along the obstructed vessel. These minute channels soon enlarge, and in the end the functional capacity of the vessel may be fairly well restored. In the case of thrombosed veins these new vessels have as a rule very thin walls, but in arteries they acquire their proper complement of muscular and elastic coats. Obstruction by a thrombus may also be relieved more quickly by the clot tearing away from part of the circumference of the vessel as the fibrin contracts. This relief may, however, be only temporary, as the conditions favour the occurrence of a further thrombosis which will again cause obstruction.

Extensive fatal intravascular coagulation may be easily produced by injecting alkaline extracts of cellular organs into the circulation. The effective part of these is presumably thrombokinase rather than the nucleo-proteid which is their best-known constituent. And the essential abnormality which underlies the conditions which favour the occurrence of thrombosis is in all probability an excess of thrombokinase at some point in the circulation. The common way in which this excess is produced is an injury to the endothelium of the vessel wall. The injury may be caused in a variety of ways. Direct mechanical injury occurs in the course of surgical operations or in bruising by external violence. The endothelium may be destroyed by heat or cold; frost-bite is associated with thrombosis. Bacterial poisons can produce the same effect. Vessels, especially veins, which are involved in an area of acute inflammation often become thrombosed in sequence to the invasion of the vessel wall by the causative organisms, and destructive inflammation of the cardiac valves by the rheumococcus is regularly followed by the deposition of thrombus at the site of injury. In more chronic conditions, such as atheroma, endothelial destruction promotes thrombosis. In many of these cases thrombokinase is furnished not only by the injured and dead cells of the vessel wall, but by the disintegration of leucocytes which are taking part in an inflammatory process and have invaded the vessel wall. This leucocytic thrombokinase, which, as we have seen, is probably the effective agent in producing clotting in shed blood, is also a factor which has to be considered in the growth and extension of thrombi. Many of the leucocytes caught in the clot show clear histological evidence of death and disintegration. If the essential reason why local injury to the vessel wall produces thrombosis is that thrombokinase is liberated from the injured cells, the localization of the thrombus requires explanation, since the thrombokinase may be properly considered to be soluble in the blood flowing past the injured spot. There are two reasons why a local injury produces a local thrombus instead of generalized intravascular clotting. In

the first place, the concentration of thrombokinase is greatest at its source of origin. And, in the second place, any injury to the endothelium provides a "point" or "points" on to which fibrin is encouraged to separate. Such "points," or "foreign surfaces," as they are more commonly called, play the same important rôle in the formation of both intra- and extra-vascular clots as they do in the separation of crystals from supersaturated salt solutions, in the formation of gas bubbles in soda-water or in the condensation of aqueous vapour from the air. As far as thrombosis is concerned, anything other than the normal intima and normal blood may act as a foreign body. Thus, a slight swelling and roughening of the intima in the early stages of a phlebitis, the ragged "ulcers" of advanced vascular degeneration, an embolus of sarcoma cells, and fibrin itself, may all induce clotting. It must not, however, be supposed that all foreign bodies inside vessels necessarily cause thrombosis. Unless sufficient thrombokinase is present, no clot will occur. And if enough thrombokinase is available, thrombosis will take place in the absence of foreign bodies. But the conjunction of the two factors is especially potent.

The rapidity of blood-flow is not of itself a cardinal factor, though it may be of considerable accessory importance. Thrombi are much commoner in veins than in arteries,* although, as far as we know, destruction of endothelium is much more frequent in arteries than in veins. The rapid blood-flow in arteries tends to sweep away the thrombus as it is formed, while in veins the mechanical conditions are more favourable, and the slower stream allows thrombokinase to accumulate to some extent at the injured spot. For all that, however, thrombi are not uncommon in arteries of normal calibre, and they are frequent where the lumen has been much reduced by disease (endarteritis). Where other conditions are specially favourable, as in acute valvular endocarditis, a very rapid stream will not prevent the deposition of a certain amount of clot, though the thrombus may never become very large. Even when the blood-stream is brought completely to a standstill, as by ligature of a vessel, clotting may be delayed for a long time, and it is impossible in such cases to altogether exclude the influence of injury to the vessel wall at the place of ligature, and some destruction of the endothelium as a whole from the cessation of its normal blood-supply. In cases where death has been preceded by a period of imperfect cardiac action and considerable slowing of the circulation, thrombosis is apt to be found post mortem, especially in the auricles. Here, too, one must consider the possibility that excess of thrombokinase has entered the circulation owing to a general impairment of the nutrition of the whole body, including the vessel

* With the reservation that, as with emboli, we know very little of thrombi which produce no obvious effects or are not easily perceptible in, *e.g.*, superficial veins.

walls and the leucocytes. On the other hand, we find a clear example of the influence of rate of flow in massive thrombi which fill aneurismal dilatations of the aorta. In the aneurism the normal endothelium is absent, and the wall is composed altogether of foreign surfaces (fibrous tissue), and leucocytes may be abundant. These conditions, however, often prevail to an apparently equal degree on immediately adjacent areas of the wall of the aorta which are fully exposed to the blood-stream, and on which thrombi are very rarely found.

A certain number of cases of thrombosis, both arterial and venous, occur in which no abnormality of the vessel wall can be clearly demonstrated. It may be that this is due to inadequate methods of examination. On the other hand, the occurrence of thrombi in association with obviously abnormal vessels is to some extent capricious, and it is not improbable that there are general changes in the thrombogenic apparatus which make clotting more easy, of a kind parallel to those which in hæmophilia produce the reverse effect. It seems likely that the cellular disintegration going on in the body is constantly furnishing a trace of thrombokinase to the circulating blood. An exaggeration of this process would lead to an increased tendency towards thrombosis generally. We have, however, no positive knowledge that this occurs. In particular, no association has been made out between the liability to thrombosis and the abundance of the factors—prothrombin, calcium, thrombokinase and fibrinogen—which go to make a clot.

So far we have dealt with definitely fibrinous thrombi occurring in fair-sized vessels. There are, however, other varieties which are met with in small arteries and veins. Small thrombi apparently formed of fibrin alone from the beginning rarely occur; others appear to consist almost entirely of blood-platelets. Hyaline thrombi of a perfectly homogeneous microscopical appearance are common. Their nature is not altogether clear, though there are no reasons for doubting that many of them are composed of fibrin which has separated out in an atypical form. Attention has already been called to the presence of such amorphous masses of fibrin in large clots. A form of capillary thrombus originating in masses of agglutinated red cells is now known to be common in the viscera in natural and experimental general infections and intoxications. It may be produced by the injection of, *e.g.*, specific agglutinating serum, ricin, some snake venoms, and occurs naturally in, *e.g.*, typhoid fever. The cells become hæmolyzed, or are hæmolyzed before they are agglomerated, lose their outlines, and eventually form a hyaline mass. Small vessels, especially actual capillaries, may also be blocked by masses of leucocytes, forming leucocytic thrombi. These occur in inflamed areas, in leukæmia, and rarely in other conditions where there is an excess of circulating leucocytes. Whether these should be called "thrombi" or "emboli" is a barren question of terminology.

# CHAPTER III

# INFLAMMATION

By E. W. AINLEY WALKER

## Introduction—The Reactive Processes (Inflammation, Infection and Immunity, Fever).

In entering on the study of pathology, the student is confronted at the very outset by a series of phenomena, whose analysis and comprehension form a foundation and basis indispensable to any true conception of the nature of the great majority of all morbid changes.

These phenomena may be termed the phenomena of *reaction*. They require consideration in two different aspects—(i.) when they appear as a circumscribed and local process; (ii.) when they concern the body generally. Their general exhibition constitutes the "reaction to infection," and will be dealt with in a later chapter; the localized events are spoken of as "inflammation."

It may, however, with advantage be at once made clear that, whether the events concerned be localized or general in their distribution, the underlying process is the same, the causal agents are in general similar, and in both cases the reaction is, in greater or less degree, associated with the development of the process known as "fever."

Moreover, local inflammation may, and often does, pass on to general infection, while general infections often—indeed, usually—lead to the production of scattered foci of inflammation, and probably always begin by being localized in some particular area of the body.

## General Description of the Phenomena of Inflammation.

### A. Inflammation in Vascular Areas.

The classical definition given by Burdon Sanderson states that inflammation is "the succession of changes which occur in a living tissue when it is injured, provided that the injury is not of such a degree as to at once destroy its structure and vitality;" or, more briefly put, it is *the response to injury*.

**Causes.**—The injury in question may be obvious and striking, or it may be at first sight obscure; and it may be brought about by a great variety of agencies. Its causes may be broadly classified under the headings of *living* and *non-living* irritants. The latter may be *physical* or *chemical* in character, and include the injurious effects of pressure, extremes of heat and cold, foreign solid substances or fluids (such as sequestra or aseptic exudates), light, electricity, Röntgen rays, and the like, or of acids, caustics, poisons, and other active chemical substances. The former comprise both *animal and vegetable micro-organisms*, and larger animal *parasites*, the *vegetable* micro-organisms constituting in themselves by far the most common of all causes of inflammation. They exert their action on the tissues either through the physical effects of their invasion, or, as is much more usual, by means of irritating chemical substances which they produce. Indeed, as implied in the definition of Burdon Sanderson, the inflammation produced by injury is dependent rather on the irritating than on the destructive properties of the causal agent, and we shall frequently find it of advantage to regard its phenomena as the expression of *reaction to irritation*.

**Cardinal Signs.**—Inflammation, then, is to be regarded as a process. It is not a state or condition, but a progression of events. And these events, at any rate in their earlier and acute stages, are usually associated with certain evident and visible changes in the condition of the part affected. These changes are frequently referred to as the cardinal signs of inflammation, and they are, when present, of considerable diagnostic value. They comprise *heat*, *redness*, *swelling*, *pain*, and *impairment of function*—the "calor, rubor, tumor, dolor, et functio læsa," of Galenic medicine. But though these so-called *signs* are useful clinically, and for descriptive purposes, it must not be supposed that all or any of them are either necessarily or invariably present in every inflammation and in all its stages. Nor can their presence be directly ascertained except in relatively superficial areas. Yet it is precisely these phenomena whose consideration forms the most natural introduction to the study of Inflammation.

**Rubor, Tumor.**—Redness and swelling clearly imply a vascular disturbance, and are due to local increase of the blood-supply and increased exudation. They are most evident in the earlier stages of acute inflammations. Along with the increased local *heat*, they were naturally the first phenomena of inflammation to excite attention, and John Hunter, the earliest accurate investigator of the subject, came to the conclusion that the events of inflammation were entirely due to vascular changes in the part concerned. He held that the fundamental change in inflammation was an increase in size or a dilatation of the existing bloodvessels of the part,

and the formation of new vessels in the affected area. Thus he says*: "The act of inflammation would appear to be an increased action of the vessels"; and again: "The part inflamed, I have already observed, becomes to appearance more vascular than when in the natural state, and it is probable that it is really so, both from new vessels being set up in the part inflamed, as well as the new and adventitious substance becoming vascular. Besides, the vessels of the part are enlarged. . . ." He seems to have recognized, moreover, that the vascular changes differed rather in degree than actually in kind from such as may occur under physiological conditions, and drew a sort of parallel between these changes and those seen in the carotid arteries of stags when their horns are growing.

Cohnheim, to whom belongs the honour of the introduction of the experimental method in pathology, was equally impressed with the importance of the vascular phenomena of inflammation, and sought to explain the process as the result of what he termed "molecular alterations" in the vessel walls. His classical investigations of the vascular events still remain among the most complete and accurate observations on the subject, and have not been modified in any essential particular by subsequent inquiry.

*Onset of Inflammation.*—If, following Cohnheim's method, the mesentery of a frog be drawn out through an abdominal incision, or its tongue be extended from the mouth, the papillæ shaved off, and the organ fixed upon the stage of a microscope, the vascular changes may be traced continuously by extending the examination over a period of several hours. Or the phenomena may be observed in the web of a frog's foot which has been lightly touched with a drop of acid or a heated wire, or from which a small piece of the epidermis has been taken with sharp scissors, thus exposing the underlying tissues to the irritant action of the air.†

Under these conditions the following series of changes in the vessels, and the circulation through them, can readily be determined:

1. At first a *constriction* of the arterioles of the part, of brief —or it may be only momentary—duration, which is rapidly replaced by

2. A condition of local *vaso-dilatation* affecting first the arteries, and later on the veins and capillaries also.

3. *Accelerated blood-flow* is observed in the dilated vessels, but this after a relatively short interval—within one to two hours—gives place to a condition of

4. *Retarded blood-flow* in the still dilated vessels. This retardation of the stream results in the widening out and gradual dis-

* Treatise "On the Blood, Inflammation and Gunshot Wounds."

† This method has the advantage that the vessels in the wound can be observed more readily than when obscured by a covering of dead epithelium, as in the other methods.

appearance of the marked "axial stream" which was visible during the period of accelerated flow. Coincident with the vascular changes there occurs a marked increase in the

5. *Exudation of fluid* from the vessels into the surrounding lymph canals and tissue spaces. This is usually accompanied by a considerable

6. *Escape of red corpuscles* from the capillaries, and by a notable

7. *Emigration of leucocytes* from the capillaries and veins, and their determination towards the site of irritation.

If the action of the irritant has been sufficiently intense, the slowing of the blood-stream may eventuate in complete *stasis* or stopping of the local circulation, when *thrombosis* may occur in the affected vessels. And so long as the irritation continues unabated, the progress of the events above recorded will continue, and will successively involve wider and wider circles round the central area of injury. On the other hand, should the irritation be removed or become sufficiently diminished in degree, the process of recovery or restoration sets in, commencing from the periphery of the affected part, and associated with phenomena spoken of as *resolution*.

**Dolor.**—Besides the *redness* and *swelling* occasioned by the vascular changes just described, the *pain* of inflammation is, for the most part at any rate, also dependent on the exudation and the vascular engorgement in the affected area, and is attributable to the increased pressure and tension which are thus exerted on the nerve endings in the region of inflammation. Accordingly, it is usually throbbing in character, the beats being synchronous with the arterial pulsation, and it is temporarily relieved by pressure over the afferent bloodvessels. Similarly, it frequently diminishes in intensity with the onset of suppuration and the formation of a definite abscess, owing, no doubt, in part to the actual destruction of nerve endings in the area affected, but also in part to the relief of tension due to softening and breaking down of tissue. Pain may also be occasioned by the pressure of exudation occurring within the nerve sheath, and in this case it is likely to exhibit a more continuous and aching character.

**Calor.**—The *heat* of inflamed parts is also due entirely to their increased blood-supply. This fact was first determined by the observations of John Hunter. In the treatise already referred to he says: "From all the observations and experiments I have made, I do not find that a local inflammation can increase the local heat above the natural heat of the animal; and when in parts whose natural heat is inferior to that which is at the source of the circulation, it does not rise so high." Hunter's results were entirely confirmed by the experiments (nearly a century later) of Cohnheim, who showed that the temperature of inflamed parts never exceeds the rectal temperature of the animal concerned.

Usually, in inflammation of any but the most limited extent, there is some degree of general pyrexia, and the blood-temperature is raised above the normal. Hence the area of inflammation may be hotter than the normal, but it is never hotter than the circulating blood. This might at first sight appear somewhat remarkable, in view of the fact that there is probably, in certain stages of the inflammatory process, at any rate, an excess of local katabolic change ; and especially so since an increased local heat production has been shown to follow local injury in certain higher plants. It is, however, merely a further evidence of the perfection of the heat-distributing mechanism in the higher animals—a mechanism adapted to the appreciably uniform distribution of the very large amounts of heat normally produced in the muscles, in comparison with which the heat production of an inflamed area must at best be relatively slight. So long as the circulation continues through an inflamed area, the heat produced in it is rapidly carried off and distributed through the body; while if a condition of stasis is established, the heat production necessarily falls, owing to the deficient supply of oxygen to the area of stagnation.

But while the temperature of inflamed parts is never greater than that of the circulating blood, it is not infrequently *lower* than the existing temperature of the body generally, and it may even be subnormal. Thus, in experimental pleurisy the inflamed pleura has been found to have a distinctly lower temperature than that of the sound side. This resulted from the fact that in the progress of the inflammation the circulation in the affected pleura had reached a condition of complete or partial stasis.

The dependence of the temperature of an inflammatory area, like that of a corresponding healthy part, upon its blood-supply was well shown in an experiment of Cohnheim, in which, while one fore-paw of a dog was caused to inflame, the other was rendered hyperæmic by the division of its nerves. After a time the temperature of the inflamed leg was found to be distinctly lower than that of the other, owing to the fact that, while in the latter the circulation remained accelerated and increased in volume, that of the inflamed leg had reached the stage of slowing and stagnation, by which not only was the local metabolism diminished, but also very much less heat was brought to the part by the circulating blood. These observations of Cohnheim were completely confirmed by Jacobson, who used instruments and methods of the greatest precision.

### B. Inflammation in Non-Vascular Areas.

The series of events which we have hitherto considered are the most evident and the most readily ascertainable phenomena of inflammation. But along with these events changes are occurring, and continue to occur, in the *tissues* of the part affected. These

concern especially the cells of the inflammatory area, the fixed tissue cells, and the wandering cells of the tissues, and also the migrated leucocytes which are collecting at the site of irritation.

These changes are best studied in the first instance in artificial inflammations of non-vascular areas, and in the reaction to irritation in non-vascular animals, where the sequence of events is not obscured by the vascular disturbances already mentioned.

If, following Senftleben, we make use of the cornea of one of the higher animals, lightly cauterizing its centre with a strong solution of zinc chloride, we may ascertain, in fortunate cases where the injury produced is only slight, and where no breach of continuity has been produced in the injured epithelium, the following series of events. In the centre of the area affected by the action of the caustic the corneal corpuscles undergo necrosis, and break down and disappear, traces of their nuclei alone remaining. Surrounding this is a zone in which the corneal cells are shrunken and altered in appearance and granular; these cells also degenerate, and ultimately break up and become dissolved, the products of their disintegration being carried off along the lymphatic channels. External to this, again, is found a zone in which the corpuscles are obviously enlarged, and their nuclei more distinct and deeply staining than usual. They are in a condition of activity and growth, and within a period of forty-eight hours may be seen to throw out processes—"regeneration spikes"—and to undergo mitotic division, replacing by their multiplication the corneal corpuscles which have been destroyed. These newly-formed cells are at a certain stage of their development quite indistinguishable in appearance from wandering cells, whether of hæmal or connective-tissue origin.

Throughout this process of decay and regeneration of corneal corpuscles, no change whatever has been visible in the nearest bloodvessels at the margin of the cornea, and no immigration of leucocytes occurs. Here, then, the reaction to irritation has concerned *only the tissue cells* of the part affected. In the central area the direct and immediate action of the irritant was to cause necrosis of the corneal cells; farther away it led to a more gradual degeneration of the corpuscles; while at the periphery its influence was merely stimulating, and led to cell-proliferation and repair of the injury. Thus, it appears that, while the degeneration and death of tissue were the immediate *consequence* of the action of an irritant, the *reaction* to irritation manifests itself in regeneration and repair.

If, in addition to the original cauterization, a small breach of continuity is made in the injured epithelium, a new phenomenon presents itself in the appearance, within a very few hours, of a small opacity in the corneal tissue just beneath the wound. Examination reveals the fact that the opacity is due to the presence of a mass of small round cells crowding the wound and the tissue spaces in its neighbourhood. These are clearly wandering cells of the

conjunctival fluid which have entered through the breach in the epithelium, for no visible change whatever has occurred in the nearest bloodvessels. They have been attracted to the area of cell destruction, probably by products of tissue degeneration, which are in part escaping through the wounded epithelium, instead of being carried off entirely by the lymph stream as in the former case. The wandering cells which invade the corneal wound are leucocytes. This can be clearly demonstrated if, using a frog for the experiment, we introduce a little finely divided vermilion into the dorsal lymph sac of the animal before injuring the cornea. The particles of vermilion are taken up by the leucocytes, which may afterwards be recognized in the corneal lesion by the colour. Here, then, we have a new factor introduced—namely, a *reaction of the leucocytes.*

The experiment may be further modified by increasing the severity of the cauterization, or by performing the operation at a point nearer to the margin of the cornea—that is to say, nearer to the bloodvessels of the sclerotic and the conjunctiva. Here, in addition to the changes previously described, a gradual invasion of the area by emigrated leucocytes coming from the nearest vascular loops may be observed. This invasion from the periphery begins to be recognizable in about twelve hours, and proceeds until the whole area is crowded with leucocytes. Of these invading cells, some are seen to degenerate and break up; others are included and absorbed by growing corneal corpuscles in the proliferating zone; others, again, are said to undergo division; but the great majority presently withdraw themselves, and within some forty-eight hours or less have entirely disappeared from the region. Meanwhile the process of regeneration proceeds as already described. Lost corneal corpuscles are replaced by the mitotic multiplication in the active area, and the surface epithelium is restored by epithelial proliferation.

This experiment finds a parallel in the observations of Metchnikoff on the tail fin of the newt. Following a slight injury produced by the brief application of a crystal of silver nitrate, a small area of epithelium and a certain number of the underlying connective-tissue cells are destroyed. In the region external to these the cells are seen to draw in their long branched processes, and to become vacuolated. At the same time the area of injury becomes swollen. The circulation in the nearest vascular loops becomes at first more active, but subsequently stasis may occur. Diapedesis of leucocytes takes place, and the migrating cells approach the centre of irritation, where they may be seen taking up the remains of the injured tissue cells, and subsequently withdrawing.

In the young axolotl embryo the tail fin is non-vascular, and here the same series of events may be observed, save that the wandering cells which approach the injured area are wandering

cells of the tissues, and not emigrating leucocytes, since there is no change in the bloodvessels nearest to the fin. If in this experiment, instead of cauterization with silver nitrate, a little finely powdered carmine is introduced into the tissues of the fin by means of a fine hypodermic needle, the invading white cells may be seen to take up and remove the particles of carmine in the same way that they remove the débris of disintegrating tissue.

### C. The Response to Irritation in Lower Animals.

From the foregoing consideration of the simplest cases which can be observed experimentally, we have ascertained the fact that in the Vertebrata the reaction to irritation always involves the tissue cells of the area concerned. Further, unless the injury is of the very slightest grade conceivable, as in the first experiment on the cornea, it also involves a determination of immigrating wandering cells to the site of irritation. Moreover, in a vascular area, or where the irritation in a non-vascular area is sufficiently severe to affect the bloodvessels nearest to its margin, vascular changes such as have already been described accompany the reaction.

The development of this reaction is clearly traceable in the lowest forms of life, and through the lower animals to its fullest manifestation in the higher types, and it appears to rest upon the fundamental properties of living protoplasm. For the completeness and accuracy of our knowledge of the comparative pathology of the subject we are especially indebted to the laborious and brilliant researches of Metchnikoff.

**Protozoa.**—Starting with the simplest Protozoa, Metchnikoff has shown that, if one of the larger amœbæ be divided by a clean cut, the wounded surfaces rapidly cease to be distinguishable, the protoplasm simply closing up over the injured part along the line of section. This is repair. Each half of the amœba now carries on a separate existence; but while the part which contains the nucleus continues to take up nourishment, and grows and proliferates in a normal manner, the other part, which is without a nucleus, dies after a longer or shorter period, and becomes disintegrated.

On the other hand, if, instead of section, injury be induced by the presence of certain chemical irritants in solution, it leads, as Miss Greenwood showed, to a remarkable change in the protoplasmic activities of the tiny organism, associated with the discharge of a series of clear or granular globules from its substance. A similar phenomenon is exhibited in the presence of anthrax bacilli by one of the varieties of leucocytes in frog's lymph, and is also occasionally recognizable in the cells of an inflammatory area in higher animals.

Indifferent particulate matter suspended in the medium in which the amœba resides is taken up by the organism when it chances to come in contact with it. A vacuole is formed around the ingested particle, and an attempt is made to digest it by the secretion into the vacuole of an acid proteolytic fluid. If the particle prove to be indigestible, it is presently extruded by the organism, and thus got rid of.

It is by a similar process that the amœba digests and absorbs the micro-organisms on which, to a very large extent at any rate, it subsists. There are, however, microbic forms which the amœba is unable to digest—probably because they are able either to inhibit the vacuole formation, or to neutralize the acid fluid and antagonize its proteolytic digestive action. In such a case the ingested organism multiplies, and rapidly invades the protoplasmic substance of its host, eventually occasioning the death of the amœba. Similar phenomena have been observed by Metchnikoff in other protozoan organisms also. And it is to be noted that, while the reaction just described in the amœba is *primarily* directed to *nutrition*, it clearly forms a *defence* of the organism against the invasion of harmful bacteria, since only on its failure can ingested microbes multiply and exert injurious action in the body of their host.

A further manifestation of the reaction to irritation in the Protozoa is exhibited in their power of withdrawing themselves from the neighbourhood of deleterious agencies; but this faculty will present itself for consideration more conveniently in the discussion of the phenomenon known as "chemotaxis."

From the foregoing observations, it appears quite clearly that in the simple protozoan forms of life the reaction to irritation is developed in two distinct directions, the one protective, and the other reparative. And the same processes can readily be traced among the Metazoa, in which they exhibit a further development and elaboration.

**Metazoa.**—In typical Metazoa there appears a subdivision of function among the cells of the body, and a differentiation into three cell layers which give rise respectively to ectoderm, endoderm, and mesoderm. And it is found that, apart from the reparative processes in which all the three cell layers may participate, the response to injury is reserved to the mesodermal cells, which retain most nearly their resemblance to the primitive unicellular organisms.

This is clearly seen in the observations of Metchnikoff on certain larvæ of echinoderms at an early stage in their development, when they consist merely of epiblast and invaginated hypoblast, with amœboid mesoblastic cells lying in the cœlomic cavity between these layers. For if living bacteria be introduced beneath the ectoderm, the mesodermal cells approach and take them up, destroying and digesting them by intracellular action. Or if the ectoderm be pierced by a sharp object, the mesodermal cells rapidly collect upon the intruding portion, and by fusing together into a plasmodial mass effectually shut it off from the general body cavity of the animal. In addition to the exclusion of the foreign body from the cœlomic cavity which is thus accomplished, there is probably also an attempt at extracellular digestion of the offending object. For in the observations on anthrax bacilli in frog's lymph already mentioned, it was noted that, after the discharge of granules by the granular leucocytes, hyaline (non-granular) leucocytes approached the bacterial clusters, forming plasmodia around them, and destroying them by a process of extracellular digestion. And among Annelidæ, in the infection of the male generative organs of the earthworm with *gregarines*, it is observed that when the latter pass into the resting stage they become surrounded by plasmodia of wandering cells, and may thus be destroyed in spite of the protection afforded them by their cyst wall.

Among the Crustacea, the important observations made by Metchnikoff

upon the water-flea (Daphnia) demonstrate again the importance of the mesodermal wandering cells in the immediate response to irritation. Thus, if the transparent carapace of this little animal receive an injury, there follows at once the collection of a mass of leucocytes beneath the lesion, and these remain *in situ* until the injured part has been restored by cell proliferation. The protective action of the leucocytes is very clearly exhibited in the course of a disease to which this animal (Daphnia) is subject, which is caused by the invasion of its body cavity by a spore-forming torula, the Monospora. The spores of this micro-organism are attacked and destroyed within the body of the host by its leucocytes; but if from their numbers and activity any spores escape destruction, they develop into torulæ, and these in turn cause an explosive breaking up of the leucocytes, and by their rapid multiplication bring about the death of the animal. The defence against the injurious action of the irritant here clearly depends on the efficiency of the wandering cells.

But in every case which is followed carefully it appears that so soon as injury ceases to progress there occurs a reaction of regeneration and repair, tending to restore the part to its original condition. This secondary reaction is not confined to mesoblastic cells, but may concern all the cell layers, and it is remarkably extensive in many of the lower forms of life. Familiar examples may be found in the restoration of lost claws in Crustacea, or the renewal of the hinder segments of divided Annelids, or in the regeneration of a lizard's severed tail. In some of the more primitive forms, the stimulus to growth resulting from irritation and injury leads to what may be spoken of as over-repair. For example, in the Hydra, if an incision be made at any point in the stem, instead of the wound simply healing up and the lost continuity of tissue being restored, a complete new oral pole and tentacles are produced at the injured point.

In higher animals, on the other hand, repair is much less extensive and much less complete, though in them also it may under suitable conditions form, even in a vascular area, the most marked and prominent feature of the response to injury. Thus, if a clean-cut incision be made aseptically into the skin and subcutaneous tissues of such an animal, avoiding any but the smallest bloodvessels, and if the surfaces be immediately brought into accurate apposition, healing takes place with a minimum of leucocyte reaction. Very few cells are actually killed by the incision, and there is practically no bleeding, the severed capillaries being closed at their division by the pressure of the knife. Only a very slight amount of exudation occurs, and the exudate rapidly coagulates and seals the wounded surfaces together. Only a slight reddening and swelling is visible about the edges of the wound. Very few wandering cells appear, since, except for the few cells destroyed by the actual section and the thin layer of coagulated exudate, no irritant or foreign body is present in the wound. Growth of the tissue cells about the wound speedily makes itself evident; the cells extend their processes across the plane of the section, and subsequently proliferate and multiply. After the lapse of forty-eight hours or so a microscopic section through the area involved may reveal very little alteration from the normal, except the evidence of hypertrophy and growth of the fixed tissue cells of the part.

**Summary.**—If now an attempt be made to summarize briefly the conclusions to which the facts hitherto recorded lead, it is

apparent at the outset that the most prominent and striking features of inflammation as usually met with in the higher animals —namely, the phenomena which are dependent upon vascular changes—are by no means either a necessary or a constant part of the inflammatory reaction. They are secondary and adjuvant, but in no way essential to the process. The response to irritation exhibits itself as one of a uniform type throughout the animal series, and it finds a parallel in the reactions of the simplest unicellular organisms. It is essentially a cellular reaction, and it presents two distinct stages, or rather phases. Of these, the former is directed to the removal and exclusion, or destruction, of the irritant; the latter, to the restoration of the injured tissues of the animal concerned. The first is a reaction, for the most part, of the mesoblastic wandering cells; the second, mainly of the fixed cells of the area involved. And where the irritation is very slight the first-named phase may be absent, or at any rate imperceptible, and the process of repair be alone in evidence.

Thus, just as the unicellular amœba exhibits two types of response to irritation—the simple healing of injured protoplasm, and the digestion or attempt at digestion of a foreign substance—so in the Metazoa the reaction is developed along two directions: first, an attack upon the irritant, and, secondly, cell proliferation to replace the injured tissue.

In the vascular parts of animals which possess a closed vascular system, the reaction is assisted by a series of changes in the local circulation, which have the effect of greatly increasing the afflux of lymph to the area of irritation, and of bringing a large number of leucocytes within the sphere of influence of the irritant, and thus assisting their determination toward the focal area. And while throughout the Metazoa the migration of wandering cells into the region of irritation is the most characteristic feature of the earlier stages of inflammation, proliferation of tissue cells and regeneration of tissue invariably accompany a successful reaction. Thus, it is clear that, just as in the Protozoa, so in the Metazoa also the response is of a twofold nature, and is directed to the repair of injury as well as to the destruction of the irritant and the prevention of further damage to the part. But these phases, though in general thus associated, may either of them be absent in particular cases, or at any rate be so brief and ill-developed as to be unrecognizable.

## The Vascular Phenomena of Inflammation.

We must now commence a more detailed examination of the events of inflammation, and may most conveniently begin with the circulatory disturbances.

**Vaso-Constriction.**—The preliminary brief *constriction* of the arterioles which was mentioned as the earliest change to be detected in the vessels of an injured area has been stated to occur after particular forms of irritation only. Thus, it is said to follow the application of dilute croton-oil to a frog's tongue or to the web of its foot, but not to occur after the action of ammonia. It is, however, probably dependent rather on the concentration, diffusibility, and rate of penetration, of the irritant employed than on its precise nature; and it is to be regarded as the direct result of a *stimulating* action of the irritant on the vessel walls, for it is not apparently dependent on the integrity of the nervous system.

**Vaso-Dilatation.**—A general *vaso-dilatation* affecting both the arteries and the veins, and to a less degree the capillaries also, rapidly supervenes in the affected area. This vaso-dilatation is to be looked on as an abolition of vascular tone of local origin. It is not a vasomotor reflex, as some have supposed, for it occurs in parts whose nerve-supply is entirely cut off. It is, moreover, greater in degree than any vaso-dilatation due to the removal of the normal constrictor impulses, as is shown by the following experiment of Cohnheim and Samuel: If the vaso-constrictor (sympathetic) nerve-supply to a rabbit's ear be divided, marked vaso-dilatation follows in the vessels of the ear; but if the part be now plunged for a short time in water at 54° C., an acute inflammation is induced, and the inflammation is accompanied by a further dilatation of the vessels of the ear.

The succession of events just dealt with—vaso-constriction followed by dilatation—and their causation, lead us to the consideration of an important physiological principle, to which it will frequently be necessary to refer in dealing with the problems of reaction—namely, that every irritant, when sufficiently diluted or weakened, becomes *ipso facto* a *stimulant*, and, *vice versa*, stimuli sufficiently reinforced or sufficiently extended in duration act injuriously, and are to be regarded as *irritants*.

Following this principle, it is easy of apprehension how the application, say, of dilute croton-oil may first lead to stimulation of the subjacent bloodvessels and induce contraction of their muscular walls, but later, as the agent penetrates in greater concentration, it may cause injury and lead to relaxation and atony. In the case of ammonia, which diffuses with extreme rapidity, the preliminary phase of constriction may pass over almost instantaneously, and thus escape detection; but if the irritant be sufficiently diluted, the constrictor effect can readily be observed. The action of ammonia is of particular interest in relation to the view which has been put forward, that the vascular changes are occasioned by a nervous "reflex" occurring in the peripheral nervous mechanisms, since physiological experiment has shown that in causing muscular

contraction ammonia acts directly on the muscle substance, and not on nerves.

**Acceleration.**—The *accelerated blood-flow* which occurs in the dilated vessels is the direct result of the local vaso-dilatation. For it necessarily ensues that, if the general arterial blood-pressure remain unaltered, the rapidity of flow must undergo increase in any area in which the peripheral resistance is diminished by a dilatation of the arterioles. It follows that the affected area now receives a greater and more rapid circulation than before, and its arterioles show a marked "axial stream" of high velocity; while the "plasmatic layer" nearest the vessel wall is practically devoid of corpuscles, since these particles are more easily kept in suspension and prevented from settling out by the rapid axial current flowing in the centre. The volume of the circulation through the part may at this period be actually doubled, as was shown by Cohnheim.

**Slowing.**—But after a longer or shorter interval the increased flow gradually gives place to a *slowing of the stream* in the dilated bloodvessels. There must therefore be coming into play some cause leading to an increased resistance to the local circulation. Such a cause might lie either in the blood itself or in the vessel walls.

That changes are occurring in the endothelial lining of the vessel walls is certainly the case. The cells of the endothelium may be seen to enlarge and proliferate, to present amœboid movements throwing out pseudopodia and projecting into the lumen of the vessel, and to exhibit phagocytic action. Moreover, they appear to acquire adhesive properties, for leucocytes, and even red corpuscles which come into contact with them, now show a tendency to remain adherent.

In the blood itself two further changes are proceeding, each of which tends to the production of increased peripheral resistance. The first of these is the enormous increase in the pouring out of lymph, which tends to increase considerably the density of the blood remaining in the vessels, and the percentage of corpuscular elements in it. This factor undoubtedly assumes importance in acute exudative inflammations involving a considerable area, in which the exudation of fluid may proceed to such an extent that not only is the blood rendered more viscous as it passes through the vessels of the inflamed part, but a condition of general hypoplasmia (or increased concentration of the blood) is set up. The second factor consists in an active accumulation of white corpuscles which come to line the inner surface of the veins, and also, as the circulation slows, the capillaries, to a somewhat less extent, narrowing the lumen of the vessels and increasing the peripheral resistance, and thus leading to further slowing of the blood-stream.

**Stasis.**—Each of these factors must produce a retarding influence on the flow of blood. But probably the alteration in the vessel walls plays the chief rôle, since Ryneck found that complete *stasis* can be artificially induced even when an indifferent fluid, such as milk, is used as a circulating medium, but that it is impossible to produce the condition at all after the activity of the endothelium has been destroyed by the circulation through the vessels of metallic poisons in solution.

It has been suggested that external pressure exerted on the bloodvessels by the exudate is an important factor in producing stasis. Certainly inflammatory œdema may, and sometimes does, lead to the occlusion of capillaries and veins, and gangrene or necrosis may follow as a consequence; but in the condition which we are now discussing there is usually no evidence whatever of any narrowing of veins by pressure from without, and stasis, when it occurs, is not associated with obliteration of the capillaries and veins, but with their distension and plugging by impacted corpuscles.*

**Exudation.**—The *inflammatory exudation* which accompanies the vascular disturbance of inflammation must now be considered. Exudation is in essence an increased lymph flow, and might conceivably be brought about by the action of some one or more of the following factors—namely, the alterations (1) in the blood-stream, (2) in the vessel walls, or (3) in the tissues of the part outside the bloodvessels.

As regards the circulation, the *mechanical* factors which determine variations in the production of lymph apart from changes in the vessel walls have been elucidated chiefly by the work of Starling. Increased lymph flow in any area follows directly on increased capillary pressure. It follows that both in the stage of active hyperæmia, and to a much greater degree in the stage of congestion with obstructed venous outflow, there will be a marked increase in the lymph formation. Active hyperæmia of itself, however, never gives rise in normal vessels to the production of a volume of lymph greater than can be carried off by the lymphatic circulation of the part; while passive congestion leading to œdema is characterized by the formation of a more watery lymph than normal. Inflammatory lymph, on the other hand, is *unusually concentrated*. Hence the vascular disturbance of inflammation by itself will not suffice to explain the inflammatory exudation.

A second factor in normal lymph production is the permeability

* It must be remembered, further, that such pressure as is here suggested would exert its first effect, not on the bloodvessels, which are kept patent by the distending force of the cardiac systole, but on the thin-walled, feebly-supported vessels of the lymphatic system, in which the lymph is flowing at a much lower pressure. So far, however, are the lymphatics from being obliterated by the pressure of the exudate that, while the blood-stream is slowing, the lymph flow from the inflamed area may be remarkably increased.

of the capillary walls. And this affects not only the volume, but also the concentration of the lymph produced. For increased permeability in any given area necessarily entails an increase in the concentration as well as increased volume of the lymph exuded under the same conditions of intracapillary pressure, since complete permeability would entail the passage of unaltered plasma from the capillaries into the surrounding tissue spaces and lymphatic channels.

The visible changes which the vascular endothelium exhibits have already been described, and it may readily be understood that the capillaries of an inflamed part, which may permit the escape of particulate matter in the form of red corpuscles, must necessarily allow the escape of a highly concentrated lymph, and even of considerable quantities of practically unaltered plasma. The altered condition of the vessel walls may therefore be admitted as a cause of the production of lymph in greater volume and in greater concentration than normal.

The influence of *permeability* and *pressure* may be taken together as affecting what is broadly termed *filtration* from the vessels into the lymphatics and tissue spaces. But under this term must be understood to be included also whatever part secretory processes may play in the passage of the lymph through the vessel walls. The controversy as to whether normal lymph production is purely mechanical, or is to some extent a secretory process, is still open, and its discussion must be left to the physiologist. But in any case it cannot be supposed that solutions pass through the living, highly active, endothelial cells unmodified except by such conditions as determine passage through dead animal membranes. Whether these cells exert secretory—that is to say, selective—action in addition remains an open question. In the meantime the possibility of such action may, for the present purpose, be regarded as included in the expression "altered permeability."

The third factor in exudation—namely, the condition of the extravascular tissues of the part—leads to the consideration of the influence of *osmosis** as a cause of the withdrawal of fluid from the vessels.

The changes which are taking place in the area of irritation are at this period in the inflammatory reaction chiefly of a katabolic and degenerative type, and lead to the production in abnormal quantity of decomposition products, many of which are known to exert considerable osmotic pressures. These substances therefore tend to dilute themselves by drawing water from the vascular system, and their increased formation is a factor of importance in the production of the exudate.

It follows, then, that all the three factors which have just been

* "Osmosis" is the term applied to diffusion between liquids separated by a membrane.

considered tend to cause increase in the volume of the lymph produced; and one of them, the increased permeability of the vessel walls, leads to the outflow of a more concentrated lymph than normal. The exudation, therefore, is attributable to increased intracapillary pressure, altered endothelium, and increased osmotic pressure in the tissues in the area of irritation, and of these the altered endothelium is probably the most important factor.

The volume of the exudation in acute inflammation was carefully investigated by Cohnheim in experiments on the hind-foot of the dog. In this animal all the lymphatics of the foot unite to join the superficial lymphatics of the leg. A cannula is placed in one of these lymphatic trunks on the outer side of the thigh, and the rate of lymph flow from it noted. An Esmarch's bandage is then applied to the foot, which is thereafter placed for some minutes in water at a temperature of 54° C. So soon as it is found that the hair on the foot is becoming loosened and easily plucked out, the foot is withdrawn from the water and the Esmarch's band removed. Inflammation of the foot speedily supervenes on the re-establishment of the circulation through the tissues injured by the degree of heat applied to the bloodless member, and the flow of lymph from the cannula increases rapidly, until in a short time its amount may reach as much as eight or ten times the normal. At the same time it becomes more concentrated and more readily coagulable, often coagulating in the cannula; and if the inflammation aroused be very acute, it may contain so many red corpuscles, escaped from the capillaries, as even to acquire a reddish tinge. In these respects it differs markedly from the abundant but dilute and only feebly coagulable lymph of passive œdema.

These results were confirmed in Cohnheim's own laboratory by the work of Lassar, who found the flow of lymph increased to eight times normal, and an increase in solids up to from 6 to 8 per cent. by weight (normal lymph containing usually less than 1 per cent.), due entirely to increase in protein content. This, it may be noted, means that the lymph stream is carrying through the tissues during any given period *fifty to sixty times* the usual amount of protein material.

It must not be supposed, however, that the whole of this amount of protein—in a percentage practically as great as that of normal blood-plasma—is necessarily present in the lymph of inflammation as it leaves the bloodvessels. A variable but by no means inconsiderable amount of it may be derived from tissue disintegration in the inflamed area, and from the destruction and solution of migrated leucocytes; and both these processes may be actively at work in inflammation. The concentration of the lymph as it leaves the vessels cannot at present in any way be determined. Probably the nearest approach that can be made is by determining the average composition of acute and rapidly-formed exudates in

serous cavities, where they receive only relatively small additions from degenerated tissue. And Halliburton, who examined pleural exudates in acute pleurisy, as compared with the fluid of simple hydrothorax of a non-inflammatory origin, found that the percentage protein of the former was nearly three times that determined in the latter, the figures for the total proteins being in hydrothorax (an average from three cases) 1·8 per cent., and in three cases of acute pleurisy 5·1 per cent., 3·4 per cent., and 5·2 per cent., respectively.

*The Metabolic Theory.*—Virchow, to whom we owe the establishment of the fundamental principle of modern pathology—namely, that tissue changes of whatever type are primarily dependent on the normal or abnormal activities of the tissue cells—attributed all the events of inflammation to an increase of local *metabolism*, which, he claimed, resulted from the action of the irritant. He regarded both the vascular disturbance and the exudation as occasioned by an increased activity of the tissue cells in the affected area. This view, however, is open to the grave objection that both the alteration in the circulation and the formation of a copious exudate are most markedly present precisely at those stages and in those types of inflammation in which tissue degeneration and rapid cell destruction, not active metabolism, are most in evidence. The stage of active growth occurs much later when the vascular disturbance and the rate of exudation are considerably reduced, and cell proliferation is no doubt *assisted* at this period by the excess of nutriment supplied in the exudate. Nor is it possible to understand how a local increase of metabolism, such as Virchow supposed, could induce the gradual and progressive slowing of the circulation, sometimes going on to actual stasis, which occurs at this stage of inflammation. On the contrary, the active hyperæmia which accompanies increased activity in normal tissues never under any circumstances leads to slowing and stagnation of the stream within the vessels, but to an increase in the rate and volume of the local circulation, which persists throughout the whole period of increased cellular activity, and on its termination again returns to normal.

A somewhat similar view to that of Virchow, though not apparently intended to be identical with it, has lately been advanced, in which it is claimed that "the needs of the tissues" form an important, and perhaps the most important, factor in the causation of inflammatory exudates. This figurative and highly teleological expression must presumably be understood to mean that the metabolism of the tissues, whether in inflammation or under ordinary physiological conditions, results in a proportional formation of some chemical substance or substances, which in some way regulate the quantity and quality of the lymphatic outflow from the bloodvessels. The existence of such substances among

the ordinary metabolites has not been proved. But it is quite conceivable, and perhaps even probable, in view of much that is at present being ascertained as to the regulation of the activity of various groups of tissue cells by products of the activity of other cells. But however this may be, such hypothetical substances could only act—the participation of nervous reflexes being proved not essential in inflammation—either by altering the osmotic pressure in the tissue spaces, or by producing changes in the blood-vessels, such as have already been discussed—namely, a local dilatation of the vessels, with increased intracapillary pressure and an increase in the permeability of their walls. Their action would therefore be indistinguishable from that of the factors which we have already considered, and the phrase employed is unnecessarily obscure. Moreover, it is quite impossible to believe that the needs of the tissues are at this period of the reaction of such extreme degree as to require the conveyance in the lymph of fifty to sixty times the usual amount of protein, yet this was the condition in the experiments quoted. Further, it would be quite incomprehensible why at a later stage of the inflammation, when cellular activity and proliferation become its most marked features, the rate of exudation should considerably diminish, as is usually the case. Rather is it to be held, as will be shown, that the feature of importance in the exudation is its tendency to dilute and carry off the irritant, whether this be dead and degenerated tissue or foreign matter, and thus to facilitate and usher in the stage of cellular activity and repair.

**Changes within the Bloodvessels.**—As the velocity of the circulation through the dilated bloodvessels begins to suffer its progressive diminution, the corpuscles which were previously swept along in the rapid "axial stream" of the arterioles gradually fall out into the "plasmatic layer" at the circumference in greater and greater numbers, following a simple hydrodynamic law, until eventually the differentiation of the axial stream is altogether lost. The factors which take part in bringing about the retardation of the blood-stream have already been discussed. Of these, the alteration in the endothelial lining of the vessels leads to such changes in its relation to the corpuscles that in the capillaries and veins the leucocytes, and even the red corpuscles, show a tendency to remain adherent when they come in contact with it, and this tendency steadily becomes more marked.

An experiment of Weber's throws an interesting light on this phenomenon. Weber ligatured the bloodvessels of a frog's leg, and thus brought the circulation through it to a standstill. On examining the web of the foot, he now observed that the corpuscles in its vessels showed no tendency to adhere to one another, but moved freely to and fro. A little mustard was then applied to a small portion of the surface of the web, thus producing irritation and local injury. Free movement ceased in the part of the web thus irritated, and the corpuscles were seen to become adherent to the vessel walls and to each other.

Further, those corpuscles which entered the affected area from the vessels beyond became similarly adherent, so that the region was soon crowded with an accumulation of corpuscles. But if any corpuscle near the periphery of the area happened to escape from the zone of irritation, it lost its adhesiveness and again exhibited free movement.

The white corpuscles are the first to be affected, and in the veins they gradually come to line the whole internal surface, forming a single, and in places even a double, layer of cells, and producing the appearance known as the *pavementing* of the veins with leucocytes. In capillaries, whose diameter but little exceeds on the average that of the individual corpuscles, the phenomenon of pavementing cannot develop itself, but the lumen of these vessels becomes more and more obstructed by the arrested leucocytes and red corpuscles. The circulation thus impeded becomes still more sluggish, and may eventually be brought to actual stasis, though this does not occur in every case, nor does it extend throughout the whole of the affected area. When the circulation is approaching the condition of stasis, it may be seen under the microscope that shortly before absolute stagnation is reached the corpuscles with which the vessels are distended exhibit an oscillating movement or pulsation, being driven forward a little by the wave of increased pressure accompanying each heart-beat, and recoiling again as the pressure falls during diastole.

If the inflammatory process has now reached its height, stasis may give way to a gradual restoration of the circulation. But if in any part the endothelial lining of the vessels has succumbed, an intravascular coagulation or thrombosis is the sequel. The area thus deprived of nourishment undergoes necrosis, and frequently becomes the centre of an abscess.

**Emigration of Leucocytes.**—Shortly after the commencement of the pavementing of the veins, white corpuscles can be seen lying immediately outside the veins and capillaries; these have emigrated from the interior of the vessels, and others may be detected in the act of passing out into the perivascular lymphatic space. The migration gradually becomes more and more marked, until the smaller vessels are surrounded by a more or less continuous covering of leucocytes, giving rise in optical section to the appearance spoken of as *margination*. Meanwhile large numbers of the leucocytes which have emigrated are passing off in the direction of the centre of irritation, travelling for the most part in a path at right angles to the course of the vessel which they have left. There is thus set up a progressive determination of leucocytes from the bloodvessels toward the inflammatory focus.

The escape of white corpuscles was first noted as a phenomenon of inflammation by Addison in 1843, and the discovery was independently confirmed by Waller in 1846, though their observations were subsequently overlooked and forgotten. But whether

the leucocytes which leave the vessels actually pass through the substance of the endothelial cells or make their way between them is even yet not certainly determined. Probably they escape either by definite stomata or through the intercellular material between the cells. And during inflammation the lines of intercellular substance may be observed to become stretched and broadened, and to present a somewhat beaded appearance, as was noted by Arnold.

The outward passage of the leucocytes is an active process. That leucocytes possess the power of active movement was first noted by von Recklinghausen, and Waller recognized the active nature of their emigration in inflammation. Cohnheim, however, in his work on inflammation, expressed a contrary opinion, and attributed their escape, as he did all the other events of acute inflammation, to alterations in the vessel walls, through which he believed them to be passively extruded by the *vis a tergo* of the circulation. In this view he was confirmed by his observation that diapedesis ceases whenever the condition of stasis is reached, and by the fact that experimental arrest of the circulation by compression of the afferent artery has the same result. The argument was, however, faulty, in that an arrested circulation necessarily entails, besides the disappearance of hydrodynamic blood-pressure, far-reaching changes in the activity of the leucocytes (and, indeed, in all the tissues of the part), owing to the altered constitution of the plasma, the deprivation of oxygen, and the accumulation of carbon dioxide and other metabolic products in the area concerned, which results from the stagnation of the blood-stream. Moreover, the arrest of emigration does not by any means invariably ensue upon the stoppage of the circulation, for Metchnikoff observed diapedesis to occur in the inflamed tail of the tadpole after the heart-beat had been stopped by the action of curare, and the blood-flow in the capillaries had entirely ceased. And were the process merely the effect of intravascular pressure, it would be as impossible to explain the well-established fact that the migration at first only affects the leucocytes (the escape of red corpuscles commencing later), as it is difficult to conceive that these cells, which are actively amœboid while within the vessels, and exhibit active movement immediately they reach the perivascular lymphatic spaces, are merely passive during their escape. The term *diapedesis*, therefore, must be literally interpreted as regards the white corpuscles.

**Escape of Red Corpuscles.**—The escape of the red corpuscles, on the other hand, is beyond doubt entirely passive. They are simply forced out through the altered walls of the dilated capillaries by the intravascular pressure. Their exit never occurs before the commencement of the leucocytic emigration, and it may frequently be observed that several red corpuscles emerge in rapid succession at the same point between the endothelial cells, and often make their

escape at a place where a leucocyte has previously penetrated the vessel wall. Even under normal physiological conditions a certain number of red corpuscles leave the bloodvessels, and appear in the lymph stream. In inflammation this number is increased in a greater or less degree in consequence of the altered conditions which now obtain—namely, the increased local pressure in the vessels resulting from increased resistance to the circulation, the distension of the capillaries, and the altered permeability of their walls. Beyond this the event has no particular significance. The increased escape of red corpuscles is not a distinctive feature of the inflammatory process, but may also be observed to occur in association with passive hyperæmia. Intravascular pressure is therefore probably the most important factor in its production.

Where the escape of red corpuscles is very considerable, and especially if the capillary walls give way in places, *petechiæ* and *ecchymoses* may be produced, as, for example, in the purpuric eruptions of certain fevers. The corpuscles which have escaped from the vessels either undergo degenerative changes *in situ*, or are carried off in the lymph stream. And in some very acute inflammations the number of red corpuscles in the lymph from the affected area may be so great that it acquires a somewhat reddish tinge, as has already been mentioned.

### Chemotaxis and Adaptation in Relation to Inflammation.

The emigration of the leucocytes constitutes one of the most striking features of the inflammatory changes in a vascular area, and not only in vascular animals, but throughout the whole animal series, the determination of wandering cells to the region involved forms the most constant character of the response to irritation. In the higher animals it concerns alike the white corpuscles of the blood and the mononuclear wandering cells of the tissues. And we must now inquire into the mechanism by which this invasion of the inflammatory area is brought about.

It has already been stated that the leucocytes are *attracted* to an area of cell degeneration. The phenomenon of attraction or "allurement" was first observed by Engelmann, who noted that various motile bacteria move rapidly towards a bubble of oxygen excreted by a vegetable organism suspended in the medium in which they reside. He also found that, if the fluid containing the bacteria were illuminated in different sections by diffused daylight and by light of various colours respectively, the bacteria were attracted by particular colours—for example, by purple—and rapidly collected in the area of purple illumination. They moved freely to and fro in the purple zone, but whenever in its movements a particular bacterium reached the boundary line between the purple and some

less congenial colour, it changed its course, and turned back again into the zone illuminated with purple light. This phenomenon was spoken of by Engelmann as *phototaxis*.

Important evidence bearing in the same direction was obtained by Stahl in an investigation on the myxomycete *Æthalium septicum*, a multinucleated plasmodial mass of protoplasm found growing in tan-pits. If this organism be placed upon a moistened surface in the neighbourhood of a little pool of infusion of oak bark, the amœboid streaming movements of the protoplasm are so directed as to bring it presently into the infusion. On the other hand, the plasmodium withdraws itself from a $\frac{1}{2}$ per cent. solution of grape-sugar, and from solutions of various salts. Pfeffer, who carefully investigated a whole series of similar phenomena, applied the term *chemotaxis* to the property in question, using the words " positive " and " negative " to denote the phase exhibited, in the one case of attraction, in the other of repulsion. Moreover, it was found that an originally negative chemotaxis can be converted into the positive phase of attraction by gradual *adaptation*. For example, a myxomycete whose supply of water is gradually and consecutively diminished will eventually send out protoplasmic processes into a salt solution which had previously injured and repelled it.

Metchnikoff, Gabritchewsky, Leber, and others, have carried out extensive observations on the chemotaxis and adaptation of leucocytes, which exhibit both these phenomena in a very marked degree. Thus, certain solutions such as malic acid, slightly soluble metals such as mercury and copper, dead animal tissue, various bacteria and their products, and many other substances, exert a positively chemotactic influence; while other substances, such as alcohol, quinine, and lactic acid, are negatively chemotactic. Moreover, it appears that the phase induced depends to a considerable extent upon the concentration of the active substance, and that a solution which exerts a negative chemotaxis will, if sufficiently diluted, yield the positive effect, and *vice versa*.

These phenomena are of both protective and nutritional significance for the organism concerned. Positive chemotaxis leads the amœboid organism which it affects to approach the bacterial or other substances that constitute its normal diet; the negative phase withdraws it from the harmful influence of noxious agencies; while the power of adaptation enables it to become habituated to what was previously unsuitable for its nourishment, or even actually injurious. And it has been shown that amœbæ, for example, can be artificially accustomed by the gradual withdrawal of their usual bacterial diet to approach, ingest, and assimilate, unwonted micro-organisms, or even to exist and flourish in the tissues of a living animal.

The wandering cells of the animal body exhibit the same properties of chemotaxis and adaptation as are thus manifested

by the lowliest independent living organisms, and in particular they are strongly influenced by the presence of bacteria, which usually appear to exercise a more or less marked positive chemotaxis. Whether any bacteria ever actually exert a negatively chemotactic influence on the leucocytes is not at present finally determined, though it is highly probable that they do so when sufficiently virulent. Certainly they may exhibit an extremely paralyzing and destructive action, associated with complete absence of positive chemotaxis, on those cells which come sufficiently within their sphere of influence. In this connection an experiment of Metchnikoff's with anthrax in the rabbit affords a valuable illustration of the relation of virulence to chemotactic action. Metchnikoff inoculated the two ears of a rabbit with virulent and attenuated anthrax culture respectively. In each case a violent inflammation of the ear resulted, but with this very striking difference, that while in the ear inoculated with the attenuated microbe there was an enormous accumulation of leucocytes, with very little accompanying fluid exudation, in the other ear, where the fully virulent bacillus was at work, there was a great effusion of clear fluid, containing only a very small number of white corpuscles.

## Suppuration.

In order to understand the manner in which suppuration is brought about, two points require to be clearly borne in mind—first, that the irritant possesses an injurious and destructive action, and, secondly, that it exerts a positively chemotactic influence. For even if the irritant be negatively chemotactic at the focus of its concentrated action, there must be a point, nearer or more remote, where, as it gradually becomes diluted, it begins to exert an attraction on the leucocytes.

In the case of a relatively mild irritant the leucocytes will be attracted to the focus of irritation itself, but they will not be seriously injured in any large numbers. They will take up some portion of the irritant or the products of its action by a process of ingestion; and it may be that they are now liberated from the influence of positive chemotaxis by the fact that they contain *within* themselves a sample of the attracting substances. At any rate, large numbers of them may presently be seen to escape into the lymphatic channels of the part, and to leave the area of inflammation by the efferent lymphatics.

But if the irritant be one of marked severity its destructive action becomes an important feature, for a considerable number of the leucocytes, which have been attracted from a distance by the irritant diffusing through the tissues in great dilution, are thus drawn within the sphere of its more concentrated and injurious action, and many of them undergo destruction and disintegration.

If, then, as the result of a continued and powerful positive chemotaxis, the determination of leucocytes towards the area of irritation becomes very great, and is associated with their widespread destruction as they approach the central region, the previously clear or faintly blood-stained exudate becomes converted by the presence of these numerous dead and decaying leucocytes, along with the broken-down and degenerating tissue of the part, into an opaque and somewhat viscid fluid. This fluid is called *pus*, and the condition is spoken of as one of *suppuration*.

Pus therefore consists of the fluid exudates plus leucocytes, dead and living, and any red corpuscles which have escaped into the area. It contains in addition products which result from degenerative changes in the affected tissues and in the immigrant cells, such as cell débris, breaking-down protoplasm, fragments of nuclei, dissolved protein, fat globules, fatty acids or soaps, cholesterin, leucin and tyrosin, and similar bodies; the fatty substances being especially prominent in chronic cases, notably so, for example, in tuberculous cold abscesses. It may contain red blood-corpuscles in considerable numbers, or substances arising from their disintegration and degeneration. It also contains the irritant and the products of its action, which in the case of bacterial irritants is a digestive action. The fibrin factors may be present, or actual formed fibrin, or, again, the products of the disintegration and digestion of fibrin. On analysis pus yields on the average from 6 to 8 per cent. of protein material, and it is usually alkaline, with a specific gravity of about 1030, and a faint mawkish odour. But it may be fœtid and give off offensive gases. Its colour is usually a pale shade of yellow, but it may be blood-stained, and in certain cases may present a blue or greenish tint. The presence in it of a "mucin-like body" is revealed by the "ropiness" produced on the addition of caustic alkali. This body is probably derived from the decomposition of cell nuclei, and is either a nucleo-albumin or an allied substance. Albumoses and peptones are very frequently present, and indicate the action of digestive ferments, usually of bacterial origin, in the *liquor puris*.

Suppuration occurring under natural conditions is *invariably* occasioned by the action of micro-organisms. Though it is possible to produce it artificially by means of chemical non-living irritants, it is *never* so produced by natural agencies. And Hüter, along with other surgical pathologists, has endeavoured to limit the term *inflammation* to conditions in which the "classical signs" are present in association with pus formation. They hold that inflammation only occurs in the presence of pyogenetic micro-organisms, and maintain, for example, that healing by the first intention takes place without the occurrence of inflammatory reaction.

Such a position is altogether out of accord with scientific observation, and is entirely untenable. However convenient it might be (and undoubtedly it would be convenient) for the purposes of clinical

surgery to accept this limitation of the term, it is quite impossible to draw any sharp and scientific distinction between a simple inflammation and one which goes on to pyogenesis. The differences are merely of degree; the process is identical in both.

Moreover, the criterion set up by Hüter—the formation of pus—is itself not necessarily conclusive evidence of the presence of bacteria—at any rate, as regards experimental inflammations. Councilman, Grawitz and de Bary, and others, showed quite definitely that substances such as turpentine and mercury, if sealed up in fine capillary tubes, sterilized, and introduced aseptically into the subcutaneous tissues of an animal, will, when subsequently liberated by the subcutaneous fracture of the little tube after the minute incision in the skin has completely healed, set up a condition of local suppuration in which the pus is found to be entirely sterile. Similar results have been obtained with silver nitrate, croton-oil, ammonia, cadaverin (an alkaloid obtained from putrefying animal matter), the tuberculin prepared from the bodies of tubercle bacilli, the dead remains of various other bacteria, and similar substances. In these cases the succession of events in the injured tissue is precisely the same as occurs in a favourable reaction to a local infection with living pyogenetic micro-organisms. It follows that the contention of Hüter and his supporters cannot be maintained, for suppuration is not necessarily associated with the bacterial infection, nor is inflammation necessarily the result of a local infection, but may have other causes.

At the same time it must be recognized that unquestionably infection plays a most important part in the great majority of inflammatory conditions, and is *always* the exciting cause of naturally-occurring pus formation. Conditions such as those obtaining in the experiments of Councilman and others just referred to cannot be reproduced by natural agencies. There are no circumstances under which strong chemical irritants such as those we have mentioned can gain access to the tissues, and accumulate locally in sufficient quantity and concentration to cause suppuration, without an abundant access being afforded at the same time to a variety of micro-organisms, which speedily assume the more important rôle in determining the subsequent history of the lesion. For all practical purposes, therefore, suppuration is to be associated with the presence of living and active micro-organisms; accordingly, it is most conveniently studied as induced experimentally by the inoculation of pure cultures of bacteria.

Probably every micro-organism which gains entrance to the tissues causes some degree of inflammatory reaction, and therefore theoretically, at any rate, might cause suppuration. But with by far the greater number of bacteria the injury produced is under ordinary conditions so slight, and the reaction of the tissues and the wandering cells so speedily destroys and removes the invading

microbe, that no visible change occurs. Thus, it was shown by Conelly and Haldane, among others, that the ordinary germs of air and water are innocuous, and that air or tap-water may be passed through the subcutaneous tissues or introduced into the peritoneal cavity of an animal without any visible* inflammation ensuing.

**Phlogogenetic** micro-organisms† are such as produce a visible inflammatory reaction, and probably all pathogenetic forms fall into this category. Moreover, the greater number of pathogenetic bacteria are known to be capable under suitable conditions of causing suppuration. But a particular group of organisms—the pyogenetic micrococci—are by far the most common causal agents found in suppurative conditions. The association of one of these, the *Staphylococcus pyogenes aureus*, with acute abscesses was first made out by Ogston in 1881, and cultures of this organism have been extensively employed in the experimental study of suppuration, and more recently by Almroth Wright in the preparation of a vaccine for the cure of acne and similar conditions.

The following account of the development of suppurative inflammation is taken in the main from the work of Hohnfeldt, who inoculated rabbits subcutaneously by the hypodermic needle with small quantities of pure staphylococcus cultures, and observed the succession of events leading to the production of an abscess.

Shortly after the inoculation has been carried out, vascular changes occur in the affected area, and the circulatory disturbance proceeds exactly in the way already described. In about four hours after the inoculation the vessels of the region were found crowded with corpuscles, and in the small veins "pavementing" of the walls with leucocytes was beginning to take place. Leucocytes were collecting in the tissue of the part, especially along the track of the inoculating needle, and of these a majority were of the mononuclear variety, the polymorphonuclear leucocytes being less numerous. It should, however, be stated that in other experiments and with other irritants the polymorphonuclear cells may be the first to appear.

Many of the connective-tissue cells in the neighbourhood were swollen and altered in appearance. The cocci injected were seen to be scattered through the tissue, and apparently multiplying. Many

* That some degree of reaction must occur in order to bring about the destruction and removal of these organisms is shown by the fact that, though they are capable of growing in lymph and tissue fluids, they do not continue to live and multiply in the body of the animal, but rapidly disappear.

† In this relation the term "micro-organism" may be taken to include all parasites which actually invade the tissues—not bacteria only, but also amœbæ, echinococci, trichinæ, etc. Blood-parasites do not cause local inflammation by their presence in the blood-stream, because so long as the circulation continues their action is not localized. But if they happen to cause a block in the circulation, the capillary area concerned becomes thrombosed, and inflammation ensues.

lay free in the lymph and tissue spaces, but a considerable number had already been ingested, some by the leucocytes, and others by connective-tissue cells.

After ten hours the conditions were similar, but were much more clearly marked. The cocci were very greatly increased in numbers, and there were large collections of leucocytes in the tissue spaces around the clustered masses of staphylococci. These leucocytes were almost entirely of the polymorphonuclear variety, but toward the margin of the affected area, farther from the cocci, the leucocytes were chiefly of the mononuclear type. In the vessels pavementing of the walls with leucocytes was marked, and margination by accumulation of migrated cells in the perivascular spaces. Diapedesis through the vessel walls was actively in evidence.

In succeeding hours the events above described became increasingly accentuated. Stasis occurred in the capillaries of the central area, and thrombosis followed, rendering the centre of the lesion extravascular. Cocci were taken up in enormous numbers by the amœboid cells, but continued to increase and multiply; the tissue spaces were dilated, and the tissue elements separated by exudation and by the masses of invading leucocytes which surrounded, and in great part concealed, the proper cells of the tissue.

By the end of the second day the region of injury had become sharply marked off from the surrounding healthy tissue. In the centre of the area the original tissue of the part had broken down, and a structure was no longer distinguishable in it. Toward the periphery, however, bundles of connective-tissue fibrillæ were still recognizable, some already more or less degenerated and faintly staining, others continuing to present a fairly normal, though much swollen, appearance. In this zone the capillaries exhibited the vascular changes of inflammation in a marked degree. External to it the appearance of the tissues and the capillaries was normal, except that here and there cocci were to be seen lying free in the lymph spaces, or contained within the endothelial cells of the capillary walls. The central area was packed with densely crowded polymorphonuclear leucocytes and cocci, the latter now lying for the most part within the cells whose nuclei were in some cases beginning to show signs of breaking up and degeneration. Toward the periphery both cocci and leucocytes became progressively fewer and fewer in number; though, as has been said, some cocci had penetrated beyond the boundary zone, and were lying in the healthy tissue outside it—a condition clearly comparable to that which obtained at the focus of infection immediately after the original inoculation.

At this period and for some days later in Hohnfeldt's experiments there was still no evidence of growth and division of any of the cells concerned in the area of reaction under observation. But about the tenth day evidence of cell division began to manifest itself. In the

interval there had been further degeneration of tissue, breaking down of polymorphonuclear leucocytes with fatty degeneration of their protoplasm, softening and liquefaction of the degenerated tissues, ingestion of cocci, and the gradual disappearance of the latter from the boundary zone of healthy tissue. The area was now the seat of a definite *abscess*, the periphery of which had begun to assume appearances characterizing the formation of what is called *granulation tissue*. This is a highly vascular tissue richly supplied with capillaries, many of them of new formation, and composed of young connective tissue containing very numerous newly-formed connective-tissue cells with large oval, single, faintly-staining nuclei. These cells are spoken of as *fibroblasts*, or *formative cells*, or are termed epithelioid from their general resemblance to epithelial cells. Many of them may be seen undergoing mitotic division.

It must be clearly understood that the periods of time here mentioned as being occupied in the development of the successive stages in the formation of an abscess afford only a broad and general indication of the course of events in a suppurative inflammation of moderate intensity. They are open to the widest variations, and they vary both with the nature of the infection and its intensity (whether of virulence or of dosage), as well as with the vigour and promptitude of the reaction evoked. Thus, for example, the whole series of changes may be so accelerated in particular cases that an abscess is already formed within as little as five or six hours from the time of infection. Similarly, the proliferative changes may be definite and marked at a much earlier period than was the case in the experiments just quoted; thus, they may, for example, be manifest within about forty-eight hours from the onset, and, as we shall see later on, in some infective inflammations cell proliferation is actually the first change to be observed, and occurs quite early, as was shown by Baumgarten in the case of tuberculosis.

Returning now to Hohnfeldt's observations. After the zone of granulation tissue had developed, the progress of the cocci was in favourable cases seen to be arrested, and repair ensued, leading to the ultimate formation of a cicatrix. But if the advance of the cocci still continued, as occurred in a number of cases, the granulation tissue was soon found to be crowded with leucocytes, which were passing through it from the vessels towards the centre of the abscess. The conditions previously observed in the central region now spread peripherally as the invasion of the cocci gradually progressed, and a new granulating zone was set up external to that which had been absorbed into the abscess, and occupying the previously healthy tissue of the surrounding area. In this way the abscess continued to enlarge until such time as the reaction of the leucocytes became successful in arresting further invasion of the tissues by the micro-organisms.

If, however, the invading micro-organisms be sufficiently virulent

and the resistance relatively feeble, the inflammatory reaction may entirely fail to localize their attack. In such a case no circumscribing zone of granulation tissue is developed, or if formed it is ill-defined, crowded with leucocytes, and penetrated by finger-like processes composed of masses of leucocytes and cocci, which extend in various directions into the surrounding tissue. With still more virulent organisms the leucocytes may actually be repelled by negative chemotaxis—though this is denied by some—or at any rate held in check, and paralyzed, if not entirely destroyed, by the invading organism which thus obtains free access to the tissue spaces and lymphatic canaliculi of the part, and as it multiplies eventually makes its way into the vessels of the lymphatic and blood vascular systems. Entering the circulation, it is carried to distant parts, and may there set up foci of metastatic inflammation, or it may develop a condition of generalized infection. In favourable cases, where the inflammatory reaction is competent, this possibility of metastasis and general dissemination is prevented by the seizure and ingestion of the micro-organisms by the immigrating cells. And to this process Metchnikoff applied the term *phagocytosis*, the cells concerned being in consequence spoken of as *phagocytes*.

### The Rôle of the Leucocytes.

Hitherto we have spoken broadly of the cells, which are attracted to the focus of inflammation by the chemotactic action of the irritant, under the term "leucocytes" or "wandering cells." And we may continue to employ the term "leucocyte" as the equivalent of "wandering cell," to include all cells which may exhibit amœboid movement and the property of chemotaxis in the course of the inflammatory reaction, provided it be clearly understood that the term does not of necessity imply a *hæmal* origin. This usage, though not that originally intended by the term, is a matter of convenience justified by custom both in pathology and in physiology. It is the more desirable owing to the fact that the large mononuclear wandering cell, which is commonly spoken of as the "large mononuclear leucocyte," and which occurs in the blood in considerable numbers, is probably not of hæmal origin at all.

The cells thus included under the term "leucocyte" or "wandering cell" are of several different types and of various origin in the higher animals. That there are different kinds of leucocytes in the blood was first definitely noted by Wharton Jones, whose observations were later on confirmed and extended by numerous observers. Systematized differentiation and classification dates from the discovery by Ehrlich of their differential staining properties with various aniline dyes, and in recent years a vast amount of attention has been centred on these cells by a large number of workers.

Here again it has been possible to recognize the association of multiplication of types and separation of functions with increasing complexity of the organism concerned, but even yet our knowledge of the comparative morphology of the leucocytes remains to a very great extent indefinite and uncertain. In the Mammalia generally and in Man they exhibit a considerable variety of forms. For the general description of the characters of the hæmal leucocytes, their place of origin, and general pathology, reference must be made to the article on the Blood. But for our present purpose we may classify the white cells of the blood in inflammation in Man under the following types—namely, the polymorphonuclear, the eosinophile, and the large mononuclear leucocytes, the lymphocytes, and the mast cells. Of these, the polymorphonuclear, eosinophile, and mast cells have their origin in the bone marrow, and have been classed together as *hæmatogenous*.

**Polymorphonuclear Cells.**—The polymorphonuclear leucocyte is *par excellence* the leucocyte of the majority of acute inflammations, especially such as are caused by pyogenetic micro-organisms, and is the characteristic cell of ordinary pus. It is very actively migratory, and is highly phagocytic, especially for bacteria. It appears to be concerned more particularly with the destruction and removal of micro-organisms and toxins,* and is believed by many observers to be an important agent in the production of antibacterial and antitoxic substances which may be set free into the exudate both by its disintegration, and probably also by a process of secretion from the intact cell. The digestive ferment through whose action it attacks the bacteria which it englobes has been named by Metchnikoff *microcytase*, in correspondence with the term *microcyte* applied by him to this variety of phagocytic cell. The group of cells in question is composed of the so-called finely granular corpuscles, whether of oxyphile, neutrophile, or basophile granulation, and supplies a majority (up to 70 per cent. it may be) of the leucocytes in normal blood. Many of these cells may escape from the inflammatory area into which they have emigrated, and return to the lymphatic channels and the bloodvessels as the intensity of the irritation diminishes. But a large number undergo destruction and disintegration in the area of inflammation, or are ingested by mononuclear leucocytes and tissue cells, or are cast off in the pus if it is discharging at a surface of the body. So far as is known, they play no part in the process of repair.

**Eosinophile Cells.**—The eosinophile cells are distinguished by coarse granules which stain brilliantly with eosin. They also are attracted to the focus of irritation at an early stage of the reaction in considerable numbers. These cells are not very numerous,

* The primary leucocyte reaction (leucocytosis) to an injection of diphtheria toxin, for example, may concern exclusively the polymorphonuclear cells.

relatively, in normal blood (1 to 5 per cent. of the white corpuscles), and in internal inflammations may be attracted to the focus in such numbers as to disappear almost entirely from the peripheral circulation. On the other hand, they are found in considerable numbers in the cutaneous vessels in inflammatory skin diseases. Clearly they play a part, and perhaps an important part, in the inflammatory reaction, but the precise nature of their rôle is still uncertain. Although occasionally they are seen to ingest bacteria, yet for all practical purposes they may be classed as non-phagocytic cells. It has been suggested that their function lies in the discharge of a secretion, indicated by a rapid diminution in the number of their granules, in the presence of an irritant. But the fact has been denied by other workers. It is also stated that they may at times proliferate and multiply within the area of inflammation, but this cannot at present be accepted as certain. Like the preceding class of leucocytes, they take no share in the regeneration of the injured tissue. Possibly they are concerned in the reaction to what may broadly be spoken of as "toxic substances," and it may be noted that their numbers are notably increased in the conditions associated with the presence of certain parasites in the alimentary canal.

**Mast Cells.**—Of the mast cells still less is definitely known in inflammation than of the eosinophile group. They are the cells with a feebly-staining nucleus, and large deeply-staining basophile granules in the cytoplasm, to which attention was first directed by Ehrlich. They are absent from the blood in normal circumstances, but appear in moderate numbers in the course of inflammation. They are slowly migratory, and they break up and disintegrate in the inflammatory area.

**Lymphocytes.**—Lymphocytes are the characteristic cells of lymphoid tissue, from which, following the lymphatic stream, they make their way into the general circulation. They are small cells with round, rather deeply staining nuclei, surrounded by a very narrow zone of protoplasm. And from them are developed *larger* lymphocytes with more abundant protoplasm, and more deeply staining round or oval nuclei. The lymphocytes are only very sluggishly amœboid, and are not phagocytic for bacteria. They migrate very much less actively, and reach the site of irritation much later than the polymorphonuclear cells. In inflammation they are seen in greatest numbers massed around the bloodvessels, either in process of emigration from the blood or arising by proliferation in the perivascular lymphoid sheath, and in some chronic inflammations are the most common type of cell to be met with. They are commonly described as "small round cells," and are not to be confounded with the perivascular exudate of larger cells sheathing the bloodvessels (seen characteristically, for example, in glanders), which is composed in part of large hyaline leucocytes

derived from the blood, and probably in part of cells arising by proliferation of the lymphatic endothelium.

**Large Mononuclear Cells.**—The large mononuclear (hyaline) cells as seen in inflammation are of various origin. One large group arise by endothelial proliferation. Another group, quite indistinguishable in appearance from the former, at any rate at certain stages of their history, arise by local proliferation of tissue cells. These mononuclear cells constitute the *macrocyte* group of Metchnikoff. They are somewhat sluggishly amœboid, and are phagocytic both for bacteria, and especially for dead and disintegrating tissue and for other cells. Those of the blood probably arise from the vascular endothelium, and may take part in the inflammatory emigration from the vessels. As has already been noted, the endothelial cells which actually form the capillary walls are seen in inflammation to exhibit remarkable activity, enlarging and projecting into the lumen of the vessel, throwing out pseudopodia, and in bacterial infection englobing the invading microorganisms. They also undergo proliferation, and are the earliest cells in the neighbourhood of the inflammatory focus to exhibit evidence of the mitotic process.

Others of these mononuclear cells arise from the endothelia of serous cavities and lymphatic sinuses. Their origin has been more particularly studied in inflammation of the peritoneum, where in a favourable—*i.e.*, non-fatal—reaction they may be present in the exudate in numbers equalling, or even exceeding, that of the polymorphonuclear leucocytes. Cornil and Ranvier, who studied the condition induced by the injection into the peritoneal cavity of dilute silver nitrate solution, showed that the endothelial cells of its lining membrane begin to exhibit great activity and growth in a few hours after the injection. In many, nuclear division occurs, so that they come to possess two or three nuclei, while others grow and enlarge to an enormous size (100 $\mu$ or more in diameter), and these are often spoken of as "Ranvier's cells."

According to Beattie, who worked with non-lethal injections of *Bacterium coli* in the guinea-pig, proliferation is evident in from eight to ten hours. The enlarged and proliferating cells project strongly from the surface of the omentum; some are seen still attached only by a narrow stalk or pedicle, and in places large, partly separated clusters of proliferated cells are found. By their liberation they give origin to the large mononuclear phagocytic cells of the exudate. In the exudate itself, from which as resolution proceeds the polymorphonuclear cells gradually disappear, until the mononuclear cells are practically the only type remaining, Beattie found every gradation in character, from small mononuclear cells *indistinguishable* from lymphocytes up to large hyaline cells apparently identical with swollen cells of the serous endothelium.

A third source of origin of mononuclear amœboid cells is to be

recognized in the fixed tissue cells of the affected part, which by their growth and proliferation give rise to cells indistinguishable from mononuclear leucocytes, and exhibiting the same activities as the latter. Thus, in the proliferation of corneal corpuscles in the boundary zone of an experimental inflammation of the cornea, the young cells formed by the division of an active corneal cell present at first the appearances of hyaline mononuclear leucocytes, and exhibit the same properties as these. And not only connective-tissue cells, but, according to Metchnikoff, the cells of much more highly organized tissues, such as muscle fibres, may give origin, when injured or when undergoing absorption, to a similar type of cell.

As regards their ultimate fate, many of these mononuclear cells undergo disintegration in the inflammatory area; others may in chronic inflammation develop into "giant cells" (either by growth with manifold multiplication of their nuclei, or by the fusion of a number of separate cells); others, again, take on an active part in the process of regeneration and the formation of new tissue.

**Plasma Cells.**—There remains to be mentioned a type of mononuclear cells to which the name of "plasma cell" has been applied, but as to whose origin and fate a considerable controversy still continues. The cell is not unlike a larger lymphocyte with abundant cytoplasm. Its cell body stains deeply with Unna's methylene blue, and within it is excentrically placed a small, rounded or oval, granular, and deeply-staining nucleus. These cells are only slightly amœboid, and are not phagocytic for bacteria; they are present in considerable numbers in inflammatory areas, but do not usually make their appearance until after an interval of several days from the onset. As to their function and destiny nothing has yet been clearly ascertained. Even their origin remains to some extent in doubt, but Adami, who points out that similar cells as well as various forms intermediate between them and ordinary lymphocytes are to be seen in the normal lymphoid and medullary tissues, believes that the majority of them are formed by proliferation of the cells of the perivascular tissue, though some may be developed from migrated lymphocytes of the blood.

The various types of cell whose origin has now briefly been indicated comprise all the amœboid migratory cells which can with certainty be classed as leucocytes of inflammation in the sense already laid down. They are derived in part from the blood, in part from proliferation in the local tissues. Of the blood cells, the polymorphonuclear, eosinophile, and mast cell groups are of an exclusively hæmal origin, and arise in the medullary tissue of the bones; while the lymphocytes and mononuclear large leucocytes arise respectively in lymphoid tissue, and by proliferation from the vascular endothelium. But besides these blood-cells other lymphocytes and other mononuclear cells of endothelial origin are found

taking part in the inflammatory reaction, which have not migrated from the vessels, but have arisen locally by proliferation in lymphoid tissue, and in endothelia other than the vascular endothelium. And with the lymphocytes may probably be classed the plasma cells. Originating *exclusively* in the local tissues is the third class of mononuclear cells, which arise by the proliferation of cells of the connective tissue, muscle, and other tissues. The large mononuclear cells, of whatever origin, constitute Metchnikoff's class of *macrophages* or macrophagocytes, while the polymorphonuclear leucocytes form the *microphages* or microphagocytes. To the fixed tissue cells which exhibit phagocytic properties, such as the cells of the various endothelia, connective-tissue corpuscles, cells of the spleen pulp, the sarcoplasm of injured muscle fibres, the term *fixed phagocytes* is applied by Metchnikoff.

**Phagocytosis.**—It has already been stated that the phagocytic leucocytes attracted to the area of irritation ingest the irritant, submit it to the action of their digestive ferments, and remove it or the products of its disintegration from the region. In an inflammation due to the experimental inoculation of a small dose of a bacterial culture of low virulence in an animal not previously the subject of invasion by that particular variety of micro-organism, this would theoretically form an accurate and complete account of what takes place. The destruction of the bacterium would remain throughout an entirely local phagocytic process, and after its completion the animal would probably be found to be just as liable as before to invasion by the same bacterium in any other portion of its body (though it might have an increased resistance locally). But with the vast majority of pathogenetic micro-organisms, and certainly in naturally-occurring inflammations due to their action, the process presents a considerably greater complexity. There is, moreover, in addition to the events occurring locally, some degree, however slight, of general reaction. Doubtless this may be almost imperceptible, but it may also be of very considerable extent even while the bacteria remain completely localized, as, for example, in an ordinary pharyngeal diphtheria.

In the course of a favourable reaction—*i.e.*, one tending to recovery—to the local invasion of a pathogenetic micro-organism, it can be shown that, in addition to what has already been stated, the positive chemotaxis and the phagocytic power of the leucocytes increase by a progressive *adaptation*; that there is an increase in the rate of leucocyte production, which gives rise to a condition of *leucocytosis* in the blood; and that the new leucocytes produced exhibit a greater positive chemotaxis and greater phagocytic power for the bacterium concerned than their predecessors. The activity of leucocyte production is indicated by the extent of the change which may occur in the marrow of the bones. The pale fatty marrow of the shafts of the long bones is rapidly converted to a

greater or less extent, and it may be entirely, into the red variety crowded with blood and rapidly proliferating leucoblastic cells. Similar activities may be exhibited in the spleen pulp, and in the substance of the lymphatic glands. Moreover, the adaptation which the new leucocytes exhibit becomes impressed on the leucocyte-producing tissues, so that they continue for a longer or shorter period after the subsidence of the local inflammation, and it may be even throughout the remainder of life, to give rise to leucocytes of increased positive chemotaxis and increased phagocytic power for the particular micro-organism in question. It has further been maintained by Wright and Douglas that special substances—*opsonins*—are developed, which, to put the matter in a single phrase, render the micro-organisms more edible; so that, for example, serum containing opsonin will enable the leucocytes of another individual or another animal to exhibit greater chemotactic and ingesting power than they naturally possess.

**Bacteriolysis.**—But the mere ingestion of bacteria does not necessarily entail their destruction, for the ingested microbes may destroy the phagocyte. And in the early stages of inflammation especially, very large numbers of leucocytes may thus be destroyed. In favourable cases, however, it is found that the digestive action of the leucocytes increases as the result of a similar adaptation to that concerned in increasing chemotaxis, until the resisting power of the bacteria is overcome and they are destroyed and digested by the leucocytic enzymes.

The fluid exudate also acquires bacteriolytic properties in the course of the inflammatory reaction, and is found to contain enzymes which can digest the bacteria, and specific bodies known as *immune bodies*, or *go-betweens*, through which the enzymes are enabled to attack the bacteria. The enzymes* in question are almost certainly set free into the fluid exudate from the bodies of leucocytes which have undergone disintegration, for Bordet and Gengou showed that, if plasma be prepared by special means without any leucocytes suffering destruction and dissolution in it during the process of their separation, the bacteriolytic enzymes are entirely absent, though they are found in quantity in ordinary serum. Such plasma also is not spontaneously coagulable; fibrin ferment, or some part of it, is absent.

According to Metchnikoff, the bacteriolytic enzymes are two in number, the one derived from the polymorphonuclear cells, the other from the mononuclear phagocytes, and he has termed them "microcytase" and "macrocytase" respectively. A considerable body of evidence tends to show further that the immune bodies are also formed by the leucocytes and leucocytic tissues, and set free into the plasma by a process of secretion or excretion. This view

* Usually referred to as the "Complement."

has been strengthened by the more recent observations of Dreyer and Ainley Walker:

By the action of these bodies—go-between and enzyme—an extracellular destruction of the bacteria may be brought about even when the intracellular attack is unsuccessful, whether because the bacteria are not ingested, or because, although ingested, they are virulent enough to kill the phagocytes.* As regards the intracellular digestion of bacteria by the phagocytes, there is, at any rate, no evidence whatever that it is different, as regards the agencies involved, from the extracellular process which has here been indicated briefly.

The effects produced by the invading micro-organisms upon the tissues, other than such trifling effects as might be caused by inert particles of similar bulk, are brought about by the action of their toxic products. These, being soluble, not only exert a local action, but gradually become diffused throughout the body, even when the bacteria remain completely localized in the inflammatory area. They are antagonized by special antidotes developed in the course of the reaction, and called *antitoxins*. These also are to be found both in the exudate and in the body fluids. But it is not within the scope of the present subject to enter on a discussion of the general reaction to bacterial invasion. This will be found fully treated in the chapter on Immunity.

It will be clear, however, from what has now been said, that the continued localization of a bacterial inflammation in the region first invaded by the micro-organisms is dependent on the success of the leucocyte reaction. Corresponding to the degree in which this is unsuccessful, and the phagocytes fail to antagonize and destroy the bacteria, the inflammation will be spreading in character, or will be merged in a general infection. And it may be noted that not only have the leucocytes the property of acquiring increased phagocytic power, but the bacteria also can become adapted and acquire the power of offering an increased resistance to bacteriolysis. Thus, the writer showed that the resistance of the *Bacillus typhosus* can be remarkably increased, and its virulence exalted, either by subjecting it daily to the lytic action of fresh blood, and making a new culture from the survivors, or by growing it for a lengthened period in a series of subcultures in the presence of its own specific antibody or go-between. In certain inflammations, for example in gonorrhœa, and in the foci of infective granulomata, the destructive properties of the phagocytic cells, and the resisting and antagonizing power of the micro-organisms, appear for a time to remain almost in equi-

* Although the parallel must not be drawn too closely, the writer of the present article believes that a general apprehension of the mechanism of extracellular bacteriolysis can most clearly be obtained by a broad comparison of the action of the enzyme and the go-between with the part played by thrombokinase and thrombogen (plus calcium) respectively in the coagulation of fibrinogen described by Morawitz.

librium, as it were, so that for a longer or shorter period the bacteria continue a parasitic existence in the living cells themselves.

### The Changes undergone by the Tissues in Inflammatory Areas.

The changes which occur in the tissues of inflammatory areas are of two opposite types—degenerative and regenerative respectively. Both types of change are frequently to be found in progress simultaneously in an inflamed part, at different points or in different orders of cells. Thus, degeneration and death of tissue may be proceeding at the focus of irritation, where the irritant is acting in concentration, while towards the periphery, where its action is of less intensity, growth and proliferation of cells may be markedly in evidence. Or, again, the parenchyma of an organ may be undergoing degenerative changes while its connective-tissue basis is proliferating. Indeed, it is necessary, and in fact essential, clearly to recognize at the outset that *stimulation and injurious irritation differ only in degree*, and that whatever is capable of causing injury will, if sufficiently diminished in intensity, exert a stimulating action; while, on the other hand, stimulation, if sufficiently intensified or long continued, becomes irritation and produces injury. Further, we must recognize that one and the same agency may have a different effect on different types of cell, according to their different resistance, or even on different cells of the same type, according as their individual condition varies at the moment; so that in one case its effect is stimulating, and causes activity and growth, while in the other it produces injury, and leads to impairment of function and degeneration.

But at any given moment the effect produced on a particular cell must be either irritant or stimulating; it cannot be both. Growth is either enhanced or it is impaired; anabolism and katabolism cannot both preponderate at the same time and place. But while these statements are quite obvious, it does not follow that the action of an irritant on a particular variety of cells is exclusively restricted either to causing degeneration or to stimulating growth. It may successively exert both influences, and in either order. It may first stimulate, and subsequently by its persistence injure; or, if intense enough, it may first occasion injury, and later on, as it becomes less powerful, or as adaptation develops in the cells affected, may merely stimulate. This principle, although sufficiently self-evident, appears to be not infrequently overlooked or disregarded in discussing the events of inflammation.

Two further considerations need to be carefully borne in mind: *first*, that for all practical purposes no irritant is of merely momentary duration, but all exert a more or less continued action;

and, secondly, that the degree of irritation at each particular point is not a constant quantity, but is the subject of continuous variation. Hence we may have at any given point, first, injury and degeneration of tissue, followed later by stimulation and proliferative changes; or, first, stimulation with active growth and reproduction of cells, and, later, injury and tissue degeneration (the irritant increasing in intensity), followed again, if the irritation lessens, by proliferation and growth. This is exemplified in the irritant effect produced by a microbic invasion. The bacterial products are developed gradually at the focus of infection; they gradually diffuse into the surrounding tissue, and again gradually diminish in intensity as the bacteria are destroyed and their products neutralized by antibodies, or diluted and washed out by the fluid exudate. Where and when the irritation is considerable, injury and degeneration result; where the products have become greatly diluted, stimulation and growth is the consequence of their action. Moreover, even at a point where the diluted irritant has already initiated proliferative changes, the gradual advance of the bacteria themselves may later on set up a focus of more powerful irritation, and cause the destruction of the proliferated cells. Thus, at every point within the sphere of influence of the irritant its intensity undergoes continuous variations, and corresponding differences occur in the effects produced. If the irritant be one of very great intensity, as in some very acute bacterial inflammations, degeneration and destruction of tissue may alone be recognizable, so long as the condition continues to progress; on the other hand, if the irritant be extremely mild, and especially if it be also discontinuous and intermittent in its action, its effect may be no more than merely stimulating, and only proliferative changes will result, as, for example, in the production of a "corn" by long-continued intermittent pressure of moderate severity.

### A. Retrograde Changes.

Wherever the degeneration and death of tissue are clearly the *direct* effect of irritation—its immediate consequence—they evidently constitute no essential part of inflammation, which is a reactive process, but are to be regarded merely as associated phenomena. Proliferation and growth are phenomena of reaction, but impairment and death are not in any sense reactive; they are merely resultant. The majority of degenerative changes seen in inflammation can therefore be excluded from among the essential features of that process, and regarded simply as associated events.

But a difficulty arises in the case of the cell degenerations which *succeed* reactive changes, and which may occur in cells that have actually been formed by reactive proliferation in the inflammatory area, or have been attracted into it in the response to irritation. Such degenerative changes appear to be veritably initiated by a

stage of activity and growth. Thus, for example, it can clearly be seen, in cases where the development of the irritating substances is very gradual—as in tuberculosis—that the first visible effect of the lodgement of bacilli at a given point is exhibited in proliferation and growth of the neighbouring cells, and only later, as the bacterial products are set free in gradually increasing quantity, does evidence of degeneration and necrosis appear. A similar condition, though one in which the progress of events is much more rapid, can be made out in the early stages of catarrhal inflammations of the mucous membranes. Enlargement and multiplication of the lining cells of the mucosa forms at first the marked and striking feature of the process. Proliferation precedes and accompanies degeneration and desquamation of the cells in question.

The same relations hold in the inflammations spoken of as "parenchymatous." This can be seen in the nephritis which may be set up during the elimination of bacterial toxins or of chemical irritants, where proliferation of the epithelium of the tubules—and particularly those portions of the tubules which are known to be especially excretory—is a prominent feature. The action of cantharidin affords an excellent example. Cantharidin is a diuretic which in small doses increases the excretory activity of the kidney; but if it be exhibited in excessive amount (or if the kidney be already enfeebled) an acute parenchymatous nephritis may result from its administration. The cantharidin circulating in the blood is gradually abstracted by the kidney cells, and its immediate effect is to cause stimulation and increased secretion. But as the drug accumulates in greater quantity in these cells, which abstract it from the blood by a selective action, its effect eventually reaches a phase of excessive stimulation—*i.e.*, irritation—and injury. It now induces not merely normal activity, but overgrowth and cell division, functional activity falling into abeyance, and later, by persistence of the irritation, leads to the degeneration and death of the exhausted cells.

Under such circumstances as those which have just been indicated, the degenerative changes are by a number of authorities regarded as being, so to speak, inaugurated and initiated by the preceding cellular activity—the *result* of the vigour and abnormal vehemence of the *response* to irritation, not the direct effect of the action of the irritant—the effect of overwork, and not the immediate consequence of injury. And hence the cell degenerations in such cases have been included as an integral part of the inflammatory process. It is, however, difficult to understand how under any circumstances we can look upon degeneration as a reaction. Such degenerations may no doubt be regarded as the *result* of the reaction, but this is merely to say that the reaction may itself produce an injury, of which there is, indeed, abundant evidence. We maintain, however, that an injury produced by whatever agency is not a part of inflammation, but its *cause*.

**The Degenerative Changes.**—The degenerations which occur in the course of inflammation, both in the fixed tissues and in the accumulated wandering cells, vary with the nature of the irritant, and to some extent with the character of the tissue affected. The commonest are the *albuminoid* and *fatty* changes. But *mucoid*, *hyaline*, and *amyloid* degeneration are also seen, the two latter occurring in the more chronic inflammations, though the amyloid change is relatively rare. In cases where the degeneration has been preceded by proliferative change, the new cells are seen to possess a more embryonic character than the normal adult cells of the tissue; degeneration has set in before they reached their full development and differentiation. This is readily observed in subacute and chronic inflammations of a tissue normally so highly differentiated as voluntary muscle. Degeneration occurs not only in cells, but also in the intercellular material, notably in the form of a marked increase in the quantity of mucin. Portions of tissue may undergo coagulative necrosis *in toto*, while digestive changes and autolysis are a marked feature in many acute suppurative conditions.

For a description and discussion of the degenerative processes the reader must refer to the chapter on Degenerations. But besides the degenerations brought about by toxic action, a considerable amount of destruction and disintegration of tissue is occasioned by the action of the digestive enzymes which may appear in the fluid exudate. Bacteria produce peptonizing ferments, and other ferments are liberated by the cell destruction which the bacteria produce, since, as we know, all animal cells contain peptic, ereptic, and probably other enzymic properties. Coagulation of fibrinogen to fibrin also frequently occurs, "thrombokinase" being liberated by the destruction of leucocytes, and by the disintegration of tissue cells in whose juices it appears normally to be present.

**Fate of the Dead Materials.**—Besides digestion and solution, with the production of albumoses, peptones, extractives, fatty acids, and similar bodies, other fates may await the degenerating cells. The final destiny of necrosed tissue varies with its situation and its mass, and with the nature of the irritant and the intensity of the irritation.

From a non-purulent, sterile exudate the materials are usually completely absorbed—fluid by the lymphatics, particulate matter by the phagocytes—and disappear more or less rapidly during the subsidence and the cessation of the inflammatory process. But large exudates, especially the fluid, may persist for a considerable period. This is partly due to simple mechanical causes, and is explainable by the fact that the volume of a cavity increases as the cube of its diameter, while the area of its surface (the absorbing surface) only increases as the square of the diameter, so that as the exudate increases in amount the disproportion between its

volume and the area of the absorbing surface becomes continually greater. Moreover, the fluid is usually under considerable tension, so that it tends to compress and narrow, if not actually to occlude, the absorbent vessels in the limiting surface.

Purulent exudates which remain encysted owing to non-absorption, and have become sterile by the destruction of the bacteria which caused the pus formation, become inspissated by the absorption of the liquor puris. The pus cells and the necrosed tissue undergo fatty degeneration, and the fatty material is sometimes completely removed by wandering cells. But where the amount of degenerated material is considerable and shut in by a well-developed wall of cicatrizing granulation tissue, it may remain encysted as a mass of fatty débris. Such a mass may persist indefinitely, or it may gradually become infiltrated with lime salts, as is frequently the case in healed tuberculosis. This infiltration with calcium salts appears to be associated with a conversion of fatty acids into soluble soaps. Possibly a stage in the process is the formation of insoluble calcium soaps, which then, reacting with the alkalies of the tissue fluids, give rise to soluble soaps of the alkaline earths and an insoluble deposit of calcium carbonate.

In the course of suppuration an extending *abscess* may eventually open up a free surface of the body or a bloodvessel, or a hollow viscus, or one of the body cavities, and so discharge its effete contents; or it may rupture under sudden pressure. All abscesses in which the condition is progressing tend to *point* in the direction of least resistance. Their contents are usually under a tension, which in some cases is considerable, and their situation is very frequently such that the tension is increased from time to time by the contraction of voluntary or involuntary muscle in the vicinity, and by other causes; in consequence of this their contents tend to be forced into those parts of the surrounding tissues which most readily yield. The influence of gravitation may in cases also be a factor of importance. In this way the pus may be caused to travel remarkable distances, infecting the tissues along the path it traverses, and forming a *sinus* which eventually opens on a mucous or cutaneous surface of the body. Along such paths very large quantities of liquor puris and disintegrated tissue, as well as active bacteria and leucocytes, may be discharged from the organism.

Most commonly in inflammation the destruction of tissue is gradual and *molecular*, as it is called, or piecemeal; but the action of a powerful irritant, or a mechanical injury, may lead to *molar* death of tissue, or *necrosis en masse*. Again, the pressure of an exudate may become sufficient to occlude the veins and lymphatics of a particular part, and thus, rapidly increased as it is by the œdema which results from such obstruction, it may eventually cut off the arterial blood-supply, with the result that the area or part concerned suffers molar death. Around the dead tissue is set up a

zone of inflammation in which softening and liquefaction proceed until the necrosed mass has been completely separated. The process by which dead material is separated, whether by a gradual molecular destruction and piecemeal removal or after death in the mass, is termed *ulceration*. When it occurs in superficial tissues the denuded inflamed surface which remains is called an *ulcer*, and any necrosed mass thrown off is called a *slough*. But in *bone* a necrosed part when separated is termed a *sequestrum*, while the process of gradual and piecemeal destruction of successive minute particles is spoken of as *caries*. If a member, or any considerable portion of an organ or complex tissue suffers necrosis *en masse* from inflammatory or other interference with its blood-supply, leading to the cessation of the circulation through it, it usually enters on a condition of *gangrene*. But the causes of molar death of tissue and the fate of the dead matter are fully dealt with in the chapter upon Local and General Death.

The line of separation of a necrotic mass passes through the demarcating zone of inflammation which is set up in the living tissue bordering on the dead substance, and is formed by the ulceration and liquefaction of the part lying in contact with the dead material, the latter acting in itself as an irritant. The separation commences at the periphery, and spreads inwards. This has been attributed to what is probably the fact, that bacterial activity is more pronounced in this region, so that pus formation and liquefaction occur there earliest. Certainly the periphery is the most open to the attack of extraneous micro-organisms, has the least blood-supply (and hence degenerates the most rapidly), and offers the least resistance to separation.

### B. Formative Changes: Regeneration of Tissue and Repair.

So soon as the strength of the irritant becomes weakened, at any point where surviving living tissue cells remain, to a degree at which its action is merely stimulating and no longer injurious, proliferative changes begin to appear in the cells.

It is evident that the conditions necessary for repair—stimulation of living and uninjured cells, and the presence of an adequate supply of nutritive material—must always exist throughout the course of inflammation at a certain variable and varying distance from the local centre of irritation. But if the irritant be spreading peripherally and increasing in intensity, it will gradually embrace within the sphere of its more violent and concentrated action successively wider and wider zones at the periphery, where its milder action had already played the part of a stimulant and initiated the preliminary stages of proliferation and the new formation of tissue. And thus as stimulation is replaced by irritation and injury, further destruction and degeneration of tissue result. On the other hand,

if the intensity of the irritation remain fairly constant, or be undergoing diminution, there will be set up at a certain distance from the focus of irritation, in the region where the necessary conditions obtain—namely, at the margin of the inflamed area—a zone of growing cells, which presently exhibit active cell division, and whose further history becomes the history of repair. The effect of dilution of an irritant on its activity may be illustrated by a reference to the experiments of Ranvier already mentioned, in which the effect of the injection of dilute silver nitrate into the peritoneal cavity of an animal was studied. In these experiments it was found that, at the end of about twenty-four hours from the time of injection, an acute inflammation, accompanied by complete loss of the lining endothelium of the peritoneal membrane, had been set up in the parts most immediately exposed to the action of the caustic fluid. But in parts more distant, and in sheltered situations where the irritant had only penetrated in very great dilution, the endothelial cells showed evidence, not of injury and destruction, but of markedly enhanced activity and growth, and within forty-eight hours some had attained a diameter of 100 $\mu$, and were becoming actively amœboid.

In the lower forms of life the term "repair" is frequently synonymous with *complete* regeneration. Even large portions of the body may be accurately and fully reproduced, and injury is followed by the re-formation of a tissue-complex identical in structure and properties with that destroyed. But in the higher animals, and especially in Man, the restoration of the more highly differentiated tissues is extremely incomplete or altogether absent, and the defect of parts which have been lost is not made good. Repair of tissue injured or destroyed in inflammation occurs for the most part by the process of *cicatrization*, with the formation of a *scar*. The simplest form of tissue—the connective tissue—which has retained a very marked facility and power of reproduction, plays the chief part, often an exclusive part, in the replacement of the lost material.

Besides connective tissue, epithelia also are capable of regenerative re-formation. A cutaneous area which has been denuded of epithelium in the course of inflammation becomes clothed again, as ulceration subsides, by the gradual spread from the periphery of proliferating cells of the germinating epithelial layer. But a lost portion of the cutis vera is replaced, not by new cutis vera, but by fibrous cicatricial tissue. The epithelia of mucous surfaces and glands may similarly be renewed after loss by degeneration due to an inflammatory condition. But complex tissues composed of highly differentiated cells of various orders, and consisting, for example, of epithelium, connective tissue, muscle, nerves, and bloodvessels, cannot be regenerated after loss by inflammation Only in healing by the primary union of clean-cut wounds can en

approach to complete restoration of the tissues be observed. And even here the immediate union is by fibrous tissue.

A gland or muscle which has lost a portion of its mass by inflammation cicatrizes. It may, indeed, subsequently regain, or partially regain, its former size, but this occurs by hypertrophy of the remaining portion as a consequence of functional stimulation, and not by the regenerative reaction of inflammation. Hence the discussion of repair in inflammation chiefly concerns the new formation of connective tissue.

The cells which develop into new connective tissue are called *fibroblasts*. These vary a good deal both in size and shape, but are on the whole rather large, and roughly spindle-shaped mononuclear cells, with oval nuclei and abundant protoplasm. It is the origin of these cells which has presented, and, indeed, still presents, one of the most difficult and controversial problems of inflammation.

A microscopic examination of young granulation tissue formed by inflammatory reaction reveals the presence in it of several types of cell. One of these clearly represents the growing fibroblasts, others are equally distinctly emigrated leucocytes of the polymorphonuclear and eosinophile varieties, whose further fate is either to retire from the area or to be ingested and absorbed by the growing cells. Finally there are cells larger than these leucocytes just mentioned, mononuclear, rounded in shape, and with relatively a large amount of cytoplasm. They are apparently large mononuclear leucocytes (of whatever origin). Do they develop into fibroblasts, or are the latter derived exclusively from the pre-existing *fixed* cells of the tissue ? The answer to this question is by no means obvious. But with the recognition of the mononuclear leucocytes as cells of endothelial and other tissue origin (in contradistinction to the hæmal leucocytes), they are brought into a much more evident relationship to the pre-existing cells of the tissues—connective-tissue corpuscles and cells of the local endothelium—which admittedly give rise to the formation of fibroblasts (in any case to a majority of them, and failing the cells in question to the whole). Hence it seems very probable indeed that a certain number of these hyaline leucocytes which find themselves in the zone of actively proliferating tissue, under the stimulus of a diluted irritant, and in the neighbourhood of vessels which supply abundant nourishment, do actually develop into fibroblasts. Cells indistinguishable from these leucocytes have been shown to exhibit all transitions from rounded to spindle-shaped and fusiform cells, and on to definite undoubted fibroblasts, and Metchnikoff has *watched* in the tadpole's tail the changes from day to day by which a wandering tissue cell became converted into a connective-tissue corpuscle. No property distinguishes the new-formed cells of connective tissue and of endothelial origin from mononuclear leucocytes of the blood ; both are slowly amœboid and form pseudopodia, and both are phagocytic ;

probably both are capable of developing into fibroblasts. Whether plasma cells and lymphocytes may also give origin to fibroblasts remains uncertain. The balance of opinion inclines at present to the negative.

It has already been stated that the tissue produced at the periphery of the inflammatory area, in which the young fibroblasts are seen in all stages of their development into mature connective tissue, is called "granulation tissue." It is first formed at the outermost limit of the region of inflammation, where the action of the irritant is least pronounced, and it begins to appear as the irritation ceases to extend, and its injurious effects subside or pass into a subacute or chronic state—that is to say, when the action of the irritant in the locality concerned is merely stimulating and no longer harmful. The new tissue is first laid down around the dilated capillaries bordering the area; that is where the supply of suitable nourishment, and especially of oxygen, is most readily obtained, and it proceeds towards the centre of the region of inflammation. Thus, around a subacute or chronic abscess, for example, it comes to form a limiting membrane—the pyogenic membrane—soft and succulent, where it abuts upon the abscess cavity, firmer and denser in its external and more fully developed portion. Where suppuration is still continuing, the tissue is still crowded with migrating leucocytes, particularly towards the surface of discharge. As inflammation commences to subside, they disappear first around the capillary loops, being probably in part devoured by growing fibroblasts; in part passing onwards towards the free surface, where they are discharged in pus or undergo destruction and solution; and in part migrating back into the bloodvessels. New capillaries are formed and pass outwards from the existing capillaries into the granulation tissue in the form of loops; upon these, again, fresh series of capillary loops become established; fusiform fibroblasts appear around the capillaries and undergo a gradual development, and thus the organization of the tissue proceeds.

**Formation of Capillaries.**—The formation of the new capillary loops occurs by budding from the endothelium of the existing capillary vessels. Rindfleisch was originally led to the conclusion that the new vessels are developed by an arrangement into hollow cylinders of "vaso-formative" cells in the extravascular tissue (similar to the method observed in the embryo), the new vessels subsequently gaining attachment to the existing capillaries where they came into contact with them, and eventually acquiring a connection with their lumen. Others have maintained that solid columns of extravascular cells acquire a lumen by a process of intracellular vacuolation, and, attaching themselves by their extremities to neighbouring capillary vessels, become the new capillaries of the granulation tissue.[5] But all the more recent evidence goes to show that the exclusive method of formation in inflammatory areas is by

"budding." The pre-existing capillary loops become enlarged and dilated, and project a little beyond the line which previously formed their outer limit. At a point on the convex surface of such a loop there appears a slight protrusion due to thickening and enlargement of the endothelial cells. This bud becomes prolonged into a protoplasmic process, at the base of which proliferating nuclei are seen. As the development proceeds the bud becomes hollowed out from the capillary lumen outwards. The protoplasmic prolongation of the bud steadily extends, and eventually meets a similar prolongation from another bud, thus forming a connection between two neighbouring capillaries, composed of proliferating endothelial cells, and ultimately penetrated by a capillary lumen. Fibroblasts appear along the sides of the new loop, and the process of organization gradually advances and extends. From the apices of the new loops fresh buds again arise, and thus the circulation is carried forward by the newly developed vessels in a series of capillary loops or vascular arches. All the new vessels originate as capillaries, merely composed of a single layer of endothelium. The later development of arterioles and veins, when it occurs, probably takes place by proliferation and growth along the capillaries of the muscular and other coats of pre-existing vessels.

If a granulating wound, or the base of a healing ulcer, from which any purulent discharge that may be present has been cautiously washed off, be closely examined, the surface appears as a bright red area covered with fine pin-point projections, not unlike a coarse velvet "pile." These little elevations are the "granulations," each one corresponding to a tiny capillary loop covered only by a layer or two of cells.

A microscopic section perpendicular to the surface of the granulating area shows that the successive ranges of capillary loops are pushed out in a direction normal to the granulating surface. The determining factor in their production would appear to be some chemotactic stimulating influence diffusing from the focus of irritation. For Councilman observed in keratitis that, if the original lesion be exactly central in the cornea, the advance of new capillaries from the periphery is uniform all round its margin. But if it have an excentric situation, the new vessels are at first seen only at the side of the cornea nearest to the lesion. Metchnikoff further believes that in the formation of new capillaries the union between the processes of neighbouring buds is brought about by mutual chemotaxis.

**Development of Granulation Tissue.**—It has been said that the fibroblasts are at first arranged along the sides of the young capillaries. In correspondence with this arrangement, it is found that the young fibrous tissue first developed is laid down in the neighbourhood and in the direction of the capillary vessels. But in the deeper, and therefore older, parts of the granulation tissue the fibroblasts have become more generally distributed through the

spaces between the capillary loops, and the arrangement of the young fibrous tissue becomes more complex, with a tendency for it to be disposed tangentially in a direction parallel to the surface of the granulating part. This interlacing of the young fibrous tissue bundles is probably of significance for the uniformity of the contraction produced later on by the shortening of the fibres as they attain maturity.

The new strands of fibrous tissue are laid down by the elongated spindle-shaped fibroblasts in the direction of their greatest length, and are probably produced by a continuous process of differentiation and splitting off of the most peripheral layer of the cell protoplasm. This gradual differentiation proceeds until little is finally left of the fibroblastic cell except its elongated and attenuated nucleus, surrounded by a thin layer of cytoplasm and a few fine protoplasmic processes representing the cell body. Some there are, however, who still incline to the view that the new fibres are of extracellular origin, and are developed from the cell by a process of secretion. The fact that the ultimate cell remnant and the fibres which it has produced are together larger than any individual naked fibroblast does not especially support this latter view, though it has at times been so interpreted. It merely implies continued anabolic activity during the formation of the fibres, which might lead equally to increased production of fibres either by increased secretion or by increased protoplasmic growth.

The new fibrous tissue formed is highly vascular, and it is developed in excessive quantity, so that the resulting scar is red and elevated. Further changes now proceed : the new fibres shorten as they reach maturity, at first rapidly, later on more and more slowly; and this contraction continues for a considerable time, so that the scar may progressively diminish in extent for many months. In the result the majority of the new vessels are so constricted as to be eventually occluded, and the red and elevated, somewhat resilient scar becomes a depressed, dead-white, shrunken, and bloodless-looking cicatrix.

Among the bundles of white fibrous tissue a certain number of elastic fibres are found. They begin to appear somewhat late in the process of regeneration—in about five or six weeks, according to L. Jores, who has studied their production with especial care—after six months they are present in considerable numbers, and may continue to increase up to a year or more from the time of injury. It is held by Jores and Miller that regeneration begins from the elastic fibres in the walls of the bloodvessels and elsewhere. But the new fibres may be developed in relation with cells which are indistinguishable from ordinary fibroblasts.

The amount of granulation tissue formed depends on the degree of persistence of that mild grade of irritation which we have recognized as the stimulus to growth and proliferation of the cells of the

inflammatory area. Thus it happens that in continuing mild chronic inflammations, especially where the irritation is insufficient to cause any marked amount of cell destruction, very considerable masses of fibrous tissue may be developed. On the other hand, the new formation of connective tissue may be almost negligible in amount in cases where irritation is reduced to a minimum, as in the healing of an abraded cutaneous area beneath a scab formed of dried exudation and blood-clot, or in the healing of an aseptic wounded surface beneath a non-irritating aseptic dressing. In such cases there may be little to record beyond the gradual spread over the healing surface of proliferating epithelium from the periphery. And little fibrous tissue having formed, there is practically no succeeding contraction.

**Giant Cells.**—It still remains to mention a particular type of cell frequently met with in the new-formed tissue of subacute and chronic inflammations, and familiar in tuberculous infections—namely, "giant cells."

These cells are multinucleated masses of protoplasm of very various size and shape. They may be larger than twice the size of a mononuclear leucocyte, or they may be twenty or thirty times that size, and even more. They are non-granular, phagocytic, and at times amœboid, for they have been seen (in lupus) to envelop and destroy elastic fibres. They undergo gradual degeneration, and take no part in the production of new fibrous tissue. Some appear to arise by growth of a single cell and repeated nuclear division without concurrent segmentation of the cytoplasm. But probably the majority are plasmodia, arising by the fusion of a number of mononuclear cells, comparable to the plasmodia formed in lower animals around foreign bodies, and to the leucocytic plasmodia produced in frog's lymph, which englobed masses of anthrax bacilli in the experiments carried out by Kanthack and Hardy. The number of nuclei varies very greatly, and is not necessarily in any close relation to the size of the cell. It may be as few as only two or three, or it may exceed a hundred; usually the number is less than a dozen. The nuclei may be crowded together in one part of the cell, or arranged crescentically or in a circle, or they may be quite irregularly distributed. In infective conditions the englobed bacteria are usually seen to lie in a part of the cell remote from the nuclei, and frequently presenting a necrotic aspect. In tubercle the appearances would sometimes almost justify a suspicion that protoplasmic degeneration and nuclear proliferation were proceeding side by side in different parts of the same cell—a condition which, if really present, would exhibit in one and the same mass of protoplasm both the injurious and the stimulating action of a very slowly diffusing irritant: degeneration in the immediate neighbourhood of the bacilli, with proliferative activity at a slightly greater distance.

**Healing of Wounds.**—The facts which have been recorded bearing on regeneration and the repair of injured tissue may now briefly be illustrated by a description of the healing of a wound, and of the repair of a simple fracture of bone.

The healing of a wound occurs either by "the first intention," by "second intention," or by "secondary adhesion." Healing by the first intention of a clean-cut superficial wound, in which no considerable vessel is divided, has already been described (p. 52). Wounds of aseptic operations involving deeper tissues and numerous bloodvessels of various calibre readily heal by the same method, provided that all bleeding has been stopped before the wounded surfaces are brought together. Bacteria, and especially the *Staphylococcus albus*, are always to be found on the external surfaces of such wounds,* but unless more actively pathogenetic organisms than the white coccus have gained access in important numbers, the slight secretion of the wound (which, as we have seen, may have bacteriolytic properties), and the phagocytic action of the wandering cells, are sufficient rapidly to render the wound aseptic and sterile. The surfaces are quickly bound together by a thin layer of coagulated "lymph," and the further progress of events goes on in the manner which has been recorded.

But if the area of the wounded surfaces be large, or if the tissues have been much disturbed and injured—perhaps torn and lacerated—or if the surfaces are not brought into proper apposition in their deeper parts, a considerable amount of exudation will occur, and to this may be added blood from capillary oozing. In such cases the wounded surfaces are kept apart by a fluid exudate, which at first, at any rate, is not highly bacteriolytic for many of the pyogenetic micro-organisms, which contains few phagocytes, and which constitutes a most excellent culture medium for bacteria. On this account a drainage-tube, or some similar device for assisting the escape of the exudate, is frequently led from the depth of the wound to the most dependent part of the skin incision, and left in place for twenty-four to forty-eight hours. In this way healing by the first intention is obtained throughout the greater part of the wound; or throughout the whole, if the tube be not left in for too long a time, and if suitable pressure be applied over the track of the tube on its removal to insure the contact of the separated surfaces.

But where the wound surfaces are kept separated by exudation or blood-clot to which micro-organisms have gained access, and in which they continue to flourish; or if the wound have been intentionally left open, a greater or less degree of suppuration necessarily occurs, and healing only takes place by granulations. The formation and development of granulation tissue has already been traced,

* It must, of course, be clearly understood that no ordinary open operation can be bacterially *sterile*, though it may in favourable circumstances be strictly *aseptic*.

and need not now detain us further. The process is completed by the gradual growth of epithelium, spreading from the edges of the wound over the granulating area. This method of healing (by the second intention) is necessarily long and tedious, especially in extensive and deep wounds, which can only heal up slowly from the bottom, and it involves a great deal of subsequent contraction owing to the large amount of scar tissue produced.

The process is shortened, and the formation of a large amount of cicatricial tissue is avoided, in the method of healing by secondary adhesion (or apposition of granulating surfaces). For if the healthy granulating surfaces of a wound be brought into contact, further access of micro-organisms is prevented, and such as are already present are soon destroyed by the bacteriolytic exudate and the phagocytes. Union then takes place between the apposed surfaces, precisely as in healing by the first intention.

**Repair of Bone.**—In repair of bone, the feature of special interest is the fact that the formative cells are not ordinary fibroblasts, but osteoblasts, and the tissue which they lay down is not ordinary connective tissue, but bone. After a simple fracture of one of the long bones, the blood effused into the medullary canal, between the fractured ends, and into the surrounding tissue, becomes coagulated (so far as it fails to escape by the lymphatics), and forms in itself a mild but persistent irritant, and an inflammation is set up. Degenerative changes occur in the clotted blood, and it is gradually removed by invading phagocytes and in the fluid exudation. Meanwhile productive changes starting from the periosteum and the endosteum lead to a process of organization and the formation of advancing granulation tissue in the clot. Similar changes proceed from the endothelium of the vessels of the bone itself, the ends of which also become opened out by a rarefying osteitis. The formative cells surrounding the capillary loops being largely osteoblasts, there results a gradual replacement of the clot by bone. That first formed is of an irregular structure, porous and very highly vascular, and lacking the normal definite arrangement in concentric rings around the Haversian canals. This *callus*, as it is called, maintains the bony fragments in position while further changes proceed in that part of it—the definitive callus—which lies immediately between the fractured ends.. Just as is the case in the inflammatory formation of fibrous tissue, the new bone of the definitive callus gradually becomes more dense, with the obliteration of a large number of the new bloodvessels and osteoblasts, and eventually the development of fairly normal Haversian systems is completed. At the same time the supporting or " provisional " callus undergoes a gradual reabsorption. If the fracture be not aseptic, union is complicated by the occurrence of suppuration and necrosis, but otherwise the process is identical with that described. But if movement is permitted freely (as in animals where the parts are

not kept fairly rigid by splints) union is not bony, the formative cells assume the characters of fibroblasts and chondroblasts, and the callus is formed largely of fibrous tissue and cartilage.

**Fibrosis.**—Continued chronic productive inflammation — that is persistent inflammation in which the marked feature is the new formation of connective tissue — leads to the condition of inflammatory *fibrosis*. The examples of this condition are of various type. In the first, which Adami has well termed *replacement fibrosis*, though the irritant is indeed different, the process is identical with that which leads to the formation of scar tissue in general, and brings about, for example, the closure of an open wound, or of an abscess cavity, which has discharged its purulent contents, and is lined by healthy granulations. It occurs in the gradual removal of an aseptic infarct, and its replacement by a fibrous scar. And this admittedly takes place by inflammation. The same series of changes is to be observed in the organization of a thrombus or an extravascular blood-clot, and in the replacement of degenerated tracts and centres in the central nervous system by new fibrous tissue. In all these cases the *irritant* at work is the dead tissue.

The writer feels compelled to recognize a similar condition in the phenomena of arterio-sclerosis. Here the change begins in a degeneration of the tunica media—whether due to increased pressure directly, or to some indirect interference with the blood-supply through the vasa vasorum—and the fibrosis is a replacement of the degenerated and dead tissue of the arterial wall.

A second type of fibrosis is the pure fibrous hyperplasia. This condition appears to be dependent on the continued action of an irritant too mild to cause degeneration of tissue, and only powerful enough to stimulate to cell proliferation. The fibrous tissue formed does not replace dead tissue, but is an addition to the tissues of the part. The condition is therefore termed "productive fibrosis."

Those pathologists who regard repair and regenerative changes as merely the sequel to inflammation, and not an integral part of the reaction, necessarily separate fibrous hyperplasia from the inflammatory process. But if the restoration of the cornea, for example, after a slight central cauterization of its surface, as in Senftleben's experiments already mentioned, be admitted to take place by inflammation; or if a mild tuberculosis be an inflammatory process; and if, as the writer has attempted to show, regenerative changes occurring in response to irritation are inflammatory and reactive changes, it is impossible to deny the same character to the fibrosis which we are now discussing. Moreover, in some of these cases the fibrosis is not a productive fibrosis from the first, but commences in acute or subacute inflammatory changes. And, on the other hand, it is possible to trace, in the action of different irritants of different intensities, an unbroken series of transitional conditions between those very acute and virulent forms of irritation,

where only destruction of tissue and degenerative changes are to be observed; through ordinary acute inflammations, where destruction is evident at first, regeneration later, as the irritant weakens; and through conditions like tuberculosis, where productive and degenerative changes alternate or proceed side by side; until finally we come to the conditions which, beginning as productive changes (as does tubercle), *remain* continuously productive, the irritant presumably never reaching a sufficient grade to cause tissue destruction, but giving rise to a persistent stimulating action. That the nature of the irritant is in many cases quite unknown is beside the point, and does not affect the question of the character of the process any more than does our ignorance, until recently, of the irritant in syphilis, and our present ignorance of the causal agent of variola or measles, prevent our recognizing the manifestations of their local incidence as inflammatory.

The productive fibroses which are most readily admitted as inflammatory are to be seen in the more chronic cases of infective granulomata—tuberculous nodules, the tubercular* masses formed in leprosy, gummata, the fibrous tumours of actinomycosis, and the like—and in the fibrous nodules formed around various blastomycetes and moulds, and the larvæ of certain animal parasites; frequently also around indifferent foreign bodies. To the same category belong the thick fibrous developments around lung cavities in tuberculous phthisis and in the walls of chronic abscesses. A similar type of inflammatory fibrosis is seen in the chronic inflammation of serous surfaces, where the new fibrous tissue laid down may in cases reach a thickness of as much as half an inch. In chronic interstitial pneumonia supervening on chronic pleurisy, it can be seen that the new fibrous tissue in the lung is laid down along the course of the lymphatics from the pleura, following the direction taken by the irritant during its absorption.

In the fibrosis accompanying chronic parenchymatous inflammations, such, for example, as chronic hepatitis leading to cirrhosis of the liver, or chronic productive parenchymatous nephritis, we appear to be dealing with an irritant powerful enough to cause degeneration of the parenchyma of the organ, but only strong enough to stimulate the less highly differentiated and more resisting interstitial tissue. Thus, in the case of nephritis, the irritant, presumably circulating the blood, injures and destroys the cells of the parenchyma—and especially, be it noted, of the excretory portions of

* It would be a great convenience in pathology and medicine if it were recognized finally as an accepted convention that the term *tubercular* should relate only to *form* and *size*, while *tuberculous* should imply the causal agency of tubercle bacilli. The word "tubercular" has always been used indiscriminately in naked-eye pathology, and by anatomists, to denote a *tubercle-like* object of any kind. *Tuberculous* may well be reserved to indicate the results of the action of that particular bacillus which is *par excellence* the tubercle-producing organism in man.

the tubular epithelium — while only reaching the connective tissue in sufficient concentration or amount to induce its proliferation. In the case of the liver, experimental evidence is available which supports this view. Thus Mertens showed that in rabbits, which were kept in an atmosphere containing alcohol vapour for a year or more, the liver became markedly cirrhotic. Hektoen, again, has isolated two bacilli which produce hepatic cirrhosis in the guinea-pig; here the condition is clearly inflammatory. And Adami has pointed out that "Picton disease" of cattle, an infective condition again, is associated with cirrhosis of the liver, probably occasioned by a bacterial toxin. Seeing that in these cases cell destruction is also going on (as well as the productive change), the fibrosis may properly be regarded as in part a replacement fibrosis; but it is only so in part, for the volume of the organ may be greatly increased as the result of the process.

In the productive fibroses, then, it may be said that we have evidence of abiding irritation of a low intensity; and just as Paget saw in the production of "corns" the effect on epithelium of the action of "intermittent pressure and irritation of moderate intensity," so we may recognize in productive fibrosis the effect of a persistent but mild irritation of the connective tissue, possibly continuous, probably in at least a majority of cases intermittent.

## The Influence of the Central Nervous System in Inflammation.

As has been mentioned in an earlier part of the present article, the integrity of the nervous system is not at all essential to the development of inflammatory reaction. Metchnikoff observed the exhibition of inflammatory phenomena in the tail of a tadpole so completely paralyzed by curare that its heart had ceased to beat, and the circulation was at a standstill—a degree of poisoning in which all centrifugal nervous impulses must have been completely blocked, even supposing they could still be initiated. And inflammation is set up as readily in areas whose nerve-supply has been divided experimentally, and in parts which have been paralyzed by disease (whether the paralysis be only of sensation, or only of motion, or be complete), as in the normal subject. Indeed, it is set up more readily under such conditions, and runs a more rapid course than when the nerve-supply of the part is normal.

Nor are the vascular events of inflammation either of nervous origin or regulated by the nervous system, as was formerly maintained. Their time relations are not those of a nervous reflex. The reaction is not prompt and rapidly developed, but it is delayed, and then only gradually—not immediately—reaches its height. Croton-oil is a powerful irritant, and may give rise to a very violent

reaction; yet, as Cohnheim showed, if croton-oil be applied to a rabbit's ear, half an hour or more may elapse before any vascular changes can be detected; and they do not then reach their highest grade at once, but only gradually after the lapse of a further interval of time, although the inflammation, when it has developed, is very acute and progresses rapidly. It follows that the circulatory disturbance is not a nervous reflex.

Neither is it controlled or regulated by the nervous system. It is a familiar fact that in a part which has lost its nerve-supply, after a period of paralytic vaso-dilatation, the arteries regain their normal calibre. If now such a part be caused to inflame, precisely the same progression of vascular events takes place as in an ordinary inflammation of a normal member. The changes in the vessels must therefore be of local origin, and they are probably idiomuscular, and in the capillaries idiocellular. For in the present state of physiological knowledge it can hardly now be possible to maintain the existence of true local reflex "centres" in peripheral ganglia or local plexuses; while the independent contractility of capillary endothelial cells, at any rate, has been definitely established by the work of Klebs. That the arterioles are capable of idiomuscular contraction and dilatation—that is to say, of functional response to changes produced in the substance of their muscle fibres by agencies of other than nervous origin—is at least highly probable. Moreover, if the vaso-dilatation of inflammation originated in a peripheral nervous reflex, it might naturally be expected that it would abolish the constriction which results from section of the vaso-dilator nerves supplying the part; but this, as we shall see, is not the case.

On the other hand, it must not be supposed that what has been adduced at all implies that vasomotor action plays no part in inflammation. On the contrary, the nervous system has a considerable influence on the progress of the inflammatory reaction, and may very greatly modify its course through the vascular nerves. Cohnheim was the first to observe that, after section of all the nerves which supply a part (thus cutting off the normal constrictor impulses, which are constantly passing down to the vessels), the succession of events in inflammation proceed more rapidly than in a part whose nerve-supply is intact. And with this observation may perhaps be associated the later discovery of Gergens and of Rütimeyer, that in a frog whose spinal cord has been destroyed the capillaries permit the transudation of a larger quantity of fluid than normal, and even allow the passage of particulate matter through their walls.

An illustration of the part which may be played by the vasomotor nerves is seen in the familiar example of the value of hot applications, especially if also moist, in increasing and accelerating the reaction, and assisting, for example, the formation of an abscess

at a site of local infection. The increased supply of blood which accompanies the reflex vaso-dilatation thus occasioned brings with it an increased supply of leucocytes, and favours the outflow of fluid exudate (itself very frequently powerfully bacteriolytic in its action), and thus aids the prevention of the spread of micro-organisms, and provides more abundantly the means for their destruction.

A more precise example of the influence of vasomotor nerves on the course of inflammation was provided by the observations of Samuel on the ears of rabbits, to which a reference has in part already been made. At the base of one pinna the nerve conveying the vaso-dilator fibres (the auricular nerve) was divided, and in the other the sympathetic (constrictor) supply. In the first case the vessels at once became narrowed, owing to the action of the unopposed constrictors; in the second the vessels dilated widely, owing to the abolition of normal constrictor "tone." Both ears were now placed for a short time in water at 54° C. After their removal from the water, both presently became inflamed. But in the ear with the constricted vessels no hyperæmia appeared, but stasis rapidly ensued, and was often followed by considerable necrosis; while in the ear with already dilated vessels the inflammation was accompanied by *further* dilatation and increased hyperæmia, and complete recovery invariably followed.

The method of experiment was modified and somewhat improved by Roger, who kept one ear intact, as a standard for comparison, severing either the constrictor or the dilator fibres in the other. Each ear was then inoculated with an equal quantity of a virulent culture of the *Streptococcus erysipelatis*. Roger then found that, when the dilator fibres had been divided, the inflammation was slower in development, and more protracted in its course than in the ear which had a normal nerve-supply, and usually ended in some loss of tissue; but if the vaso-constrictor nerve was severed the condition appeared more quickly, ran a more rapid and more favourable course, and terminated sooner in that ear than in the other.

But although the nervous system is *not essential* to the development of inflammation, and only affects its progress through the agency of normal vasomotor impulses, yet it has been thought to influence the *liability* of tissues to become inflamed, and even under special circumstances to *initiate* the process. This view is to a large extent bound up with the somewhat worn-out physiological conception of special trophic nerves governing the nutrition of the tissues, and thus indirectly modifying their resisting power. The existence of trophic nerves, however, becomes increasingly dubious. if the view be not now altogether discarded by physiologists. We are accustomed more and more to regard the cells of the body as self-regulating in their nutrition and growth, and affected only in

their metabolism by the requirements of their own activity, and the competition of neighbouring cells for whatever supply of nutritive material is available—and under normal conditions this is probably always present in excess of the immediate needs. Increased or diminished nutrition in normal adult tissues properly supplied with food only follows upon increase or diminution of functional activity, the stimulus to which is either physiological and normal or pathological and abnormal, and may, indeed, be brought about through the nerves. But such nerves are the ordinary centrifugal nerves which regulate functional activity of various kinds, not special fibres of exclusively nutritional intention.

All the evidence which seemed to point to special trophic influences readily admits another and a simpler explanation. The tendency of the eye, for example, to undergo severe and destructive inflammation after the removal of the Gasserian ganglion, and the well-known liability of paralyzed limbs, and parts from which sensation has been lost, readily to become inflamed, is sufficiently explained in the former case by the loss of sensation, which prevents the appreciation, and consequent removal, of irritating matter which may gain access to the conjunctival sac; in the latter case by a similar loss of the defensive influence of discomfort and pain (which normally lead unconsciously to change of position and so on, for the relief of local pressure, for example), and by the lowered vitality and resisting power of tissues, in which there is a diminished circulation and a condition of atrophy from disuse. If the eye be kept closed and covered, or the paralyzed limb protected from pressure and undue lowering of its temperature by soft wrappings, inflammations do not arise. It is, in fact, by suitable response to afferent impressions—and notably the primitive impressions of pain and discomfort, and the extremes of heat and cold—that the body tends to protect its surfaces from irritation and injury. And that the duty of conveying notice of such irritation to the central nervous system is assigned to the more elementary sensory mechanism, which Head terms *protopathic*, rather than to the higher *epicritic* type of sensation, is evidenced by the observations of Head, Russell, and Sherren, that while the protopathic nerves remain intact the skin and other tissues remain normal, and that where, following injury of the protopathic fibres, changes have occurred in the skin and nails, or an existing wound is healing indolently, healing is promptly carried out, and the tissues rapidly assume their normal appearance coincidently with the return of the protopathic sense, though epicritic sensibility still remains for long entirely absent.

Whether the nervous system under any circumstances *initiates* an inflammation in a peripheral area is a more difficult problem. Head and Campbell showed that the condition of herpes is associated with an inflammatory condition of the corresponding posterior root ganglion, and they hold that the nervous lesion is the prime factor

in the development of the peripheral condition. The causal agent of the condition remains unknown, but the appearances would perhaps suggest a bacterial origin. In any case there remains as a possible explanation—besides the theory of a nervous origin of the skin lesions—the suggestion that the herpes may be secondary to sensory disturbance at the periphery resulting from the inflammation in the ganglion, and therefore similar in origin to the cases just discussed above. Herpes of the lip associated with acute pneumonia remains a difficulty, as do the "sympathetic" inflammations sometimes seen to arise in an area whose nerves are branches of the nerve which supplies an already inflamed part, or are derived from the same region of the spinal cord. A similar example is to be found in cases of sympathetic panophthalmitis. Possibly in some of these instances further information may be gained by fuller investigation of the perineural lymphatics, which afford a ready channel for the spread of irritants; possibly in others the hypothesis of sensory disturbance is at least as helpful as the nervous theory.

Yet another case in which inflammation has been attributed to nervous agencies is that of the nephritis which may succeed a reflex suppression of urine, of whatever origin. But here the inflammation is doubtless due to the injury of kidney tissue occasioned by the reflex vascular disturbance. In those cases which follow the introduction of a catheter, it is certainly in the great majority of instances a septic process, due to the introduction of micro-organisms with the catheter. And in neither case is the immediate irritant a nervous impulse.

Those, however, who maintain the theory of the possibility of a nervous origin in inflammation rely especially on certain cases of hypnotic suggestion, in which the suggestion that a piece of red-hot iron had touched the hand has been followed speedily by appearances quite indistinguishable from a burn—immediate redness followed by considerable exudation and swelling. But the exudation never becomes purulent, and there is no evidence of local chemotaxis of the leucocytes—that is to say, no evidence of any marked injury of the extravascular tissues of the part. This in itself might suggest that the phenomena were of vascular origin—brought about by the influence of the vasomotor nerves—and therefore not a true inflammatory reaction (except in the eyes of those who still adhere to Cohnheim's theory of the nature of inflammation). And though, as has been pointed out at an earlier period, active hyperæmia never under normal conditions leads to a greater lymph production than can be accommodated in the lymphatic spaces, and carried off without the production of local œdema, yet it seems quite possible that abnormal extreme vaso-dilatation strictly localized in a small area, and therefore not affecting the general blood-pressure, might lead to so great an amount of

transudation as to cause a marked degree of swelling and œdema. In the experiments of Gergens already mentioned, total abolition of constrictor tone led to increased exudation, and the escape even of particulate matter from the vessels, in spite of the enormous fall of blood-pressure which accompanies destruction of the spinal cord. And it may therefore reasonably be maintained as a possibility, that the extremely powerful stimulus of hypnotic suggestion might produce in a subject (for whom the idea of the application of a red-hot iron would contain the idea of pain and subsequent vascular disturbance) so extreme a condition of local vaso-dilatation in a limited small area as would in itself entail the development of œdema. Accordingly the writer is inclined, at any rate, for the present, to regard so-called "inflammation by hypnosis" as strictly comparable to other hypnotic and hysterical phenomena, in presenting a close mimicry of a diseased condition rather than the condition of disease itself, and to consider the possible initiation of inflammation by the nervous system as "non-proven."

### Systemic Disturbances associated with Inflammation.

The systemic disturbances which may be associated with inflammation, especially when it is widespread and severe, are of various orders. Most of them have as yet been insufficiently investigated, and many of them are but little understood; though the majority are clearly brought about by the absorption of toxic products or similar substances from the area involved in inflammation.

The changes which occur in the constitution of the blood have been the most closely observed. In acute inflammation of any considerable extent the continued exudation leads to a marked lessening of the fluidity of the blood, and this *apoplasmia* is to some extent proportionate to the size and vascularity of the part involved. Quite apart from any question of loss of fluid from an open wound, or its accumulation in a body cavity, more fluid leaves the vessels than is returned to them by the lymphatic circulation. And the resulting increase in the specific gravity of the blood may persist for several days. This increased viscosity of the blood, it will be remembered, was suggested as one factor in producing a tendency to stasis in the inflammatory area itself.

In the leucocytic count of the blood a notable biphasic change takes place. There is, in the presence of powerful irritants at any rate, a primary phase of diminution in the number of leucocytes in the peripheral blood-stream — a condition of *leucocytopenia*, or leucopenia, as it is often called—possibly depending for its extent upon the relative virulence and chemotaxis of the irritant; but *not* of necessity an evidence of the destruction of leucocytes, since, as Muir and others have shown, the leucocytes may be collected in

particular areas of the circulation, and especially in the vessels of the lungs, and therefore correspondingly reduced in numbers in the cutaneous vessels from which the count is ordinarily made. The stage of leucocytopenia may be very brief, and it is followed by the appearance of *leucocytosis*, which, indeed, may be present even within an hour of the onset of inflammation; though in virulent infections it may be considerably delayed, and may even fail entirely in extreme cases.

With the leucocytosis, and, indeed, standing in causal relationship to the increase in the number of *hæmal* leucocytes, proliferative changes of great activity are exhibited in the bone marrow (see article on Blood). These changes may probably be attributed to a stimulating and chemotactic action exerted by greatly diluted products of the irritant which reach the circulation, and so the bone marrow from the inflammatory focus—an action comparable to that by which, as already suggested, local cell proliferation and regenerative changes are determined at a later period, when the irritant and its diffusing products have become much weakened.

The different kinds of leucocytes are not increased proportionately to their relative numbers in the normal blood, and, according to most observers, it is chiefly the polymorphonuclear cells which show a marked increase. The leucocytosis of uncomplicated tuberculosis, however, is said to be dependent, not on marrow changes, but on an increase of the mononuclear cells, and particularly of the lymphocytes. Probably the nature of the increase is determined to a great extent by the character of the particular irritant, and possibly to some extent by its situation also.

T. E. Holmes, who with the writer made a long series of observations at Guy's Hospital on the leucocyte reaction in rabbits following the local injection of various substances, observed remarkable differences in the character of the leucocytosis induced in different cases. The reaction to dissociated cells of glandular organs, and to red blood-corpuscles, was especially interesting, being in every case a pure mononuclear leucocytosis, which usually reached its maximum about the sixth day after the inoculation, when the number of mononuclear leucocytes per cubic millimetre of blood amounted to as many as ten or fifteen thousand. On the other hand, we found that the reaction to such a substance as diphtheria toxin, for example, was an enormous polymorphonuclear leucocytosis, followed one or two days later, if the animal survived, by a gradual increase in the mononuclear count which reached a considerable height, and which we suggested might have a similar relation to the removal of dead polymorphonuclear leucocytes that the mononuclear leucocytosis in the former case would appear to have to the removal of the dead animal cells injected. The injection of living micro-organisms produced in general a leucocytosis mainly of the polymorphonuclear type, the mononuclear leucocytes often increasing later on; while with *dead* bacteria there was a marked tendency to a mixed leucocytosis, in which the mononuclear cells were markedly in excess of the polymorphonuclear. The subject, however, requires a fuller investigation.

*Fever* of a greater or less degree is a usual accompaniment of an inflammatory reaction of any important severity and extent. And

it is now well known that both in the process of the absorption of fibrin and in the normal metabolism of bacteria albumoses are produced which can give rise to *pyrexia* by interference with the thermolytic mechanism. A *disturbance of metabolism*, also occasioned by inflammatory or bacterial products, completes the process of fever. But for a full discussion of the process of fever the reader must refer to the article dealing with that subject.

Disturbances of the central nervous system may also frequently be met with in inflammation, whether due to excessive pain, or attributable to poisoning by toxic substances absorbed from the area of inflammation. Little is known of these substances up to the present, and little can here be said as to their nature and their mode of action, but they may give rise in marked degree to the condition now usually spoken of as *shock*.

In continued suppuration with a prolonged discharge of large quantities of pus, a condition of pronounced *anæmia* may be produced, and degenerative changes—notably amyloid degeneration—make their appearance, and may become extreme. They are probably to be attributed in part to the absorption of cell poisons, and in part to the starvation of the tissues consequent on the continued drain upon the system (see articles on the Blood and on Degenerative Processes).

## The Varieties or Types of Inflammation.

Although the process of inflammation is invariably the same—namely, a defensive and "scavenging" reaction of the wandering cells, and a regenerative reaction of the tissue elements—yet its manifestations exhibit very great apparent variety according as one or the other feature of the process, and one or another stage of the reaction, is brought into prominence or sunk into insignificance, as the case may be, by the separable accidents of particular instances of the condition. There is only *one kind* of inflammation, but it offers a variety of types and presents itself in many varying degrees. Thus, we speak of *acute* and *chronic* inflammations according to the intensity of the irritation, the degree of reaction produced, and the duration of the process; of *serous*, *sero-fibrinous*, *fibrinous*, *hæmorrhagic*, and *suppurative* (or *purulent*) inflammations, or of *catarrhal* and *membranous varieties*, according to the character of the exudate; of *interstitial* and *parenchymatous* inflammation according as the effects of the process are most apparent in the increase of interstitial tissue or in the degeneration of the parenchyma of the organ concerned; and of *destructive* or *productive* inflammation, according as the destruction or the new formation of tissue forms its prominent feature. In *serous* inflammation the exudtaion of fluid is the striking feature, as, for example, in a serous pleurisy. In the *sero-fibrinous*

form affecting serous membranes fibrin is produced and is deposited on the denuded serous surface, while the cavity becomes filled with exuded fluid. In the *fibrinous* or "dry" variety the fluid exudate is at a minimum, while the surface of the inflamed membrane becomes clothed with a thick and often shaggy layer of fibrin. Where the amount of blood in the exudate becomes considerable the inflammation is termed *hæmorrhagic*, and when pus is produced the term *suppurative* or *purulent* is employed. In inflammations affecting mucous surfaces the term *catarrhal* is made use of when the leading feature is the proliferation, degeneration, and desquamation of the living epithelial cells (catarrhal cells) and the remarkably increased discharge of mucus; while if necrosis and death of the lining cells of the membrane, the deposit of fibrin among and upon them, and its infiltration with leucocytes are prominent, and result in the production of a "false membrane" covering the surface, the inflammation is termed *membranous*. But all such attempted classifications and distinctions are largely artificial in character, and they are also necessarily incomplete. Moreover, many of the various terms employed are not mutually exclusive. Here, however, we have only to direct attention to the chief *causes of variation* in the type of the reaction.

Accordingly, we may note that inflammation varies in its salient features with the nature and position of the tissue involved; with the nature of the irritant; and with the intensity and duration of the irritation. It varies also with the variations in the different factors which make up the individuality of each particular subject. And each of these modifying influences plays its own appropriate part in each particular case of inflammation.

As regards the *nature of the tissue* affected, much depends upon its degree of differentiation, highly organized tissues being less resistant to injury, becoming more readily inflamed than structures where the differentiation is less, and exhibiting under the same irritation much more extensive degeneration and destruction of tissue than do the latter. Thus, for example, one and the same irritant acting on the liver may produce degeneration of the hepatic cells, while leading to productive changes in the connective tissue, as in the case of hereditary syphilis.

As we have already seen, the vascularity or non-vascularity of the part concerned leads to marked differences in the more striking features of an inflammation. And the degree of vascularity of the area affected plays an important part in determining both the course and the duration of the inflammatory reaction produced by any given irritant. Where the blood-supply is free, there is greater exudation, readier access of phagocytes, more rapid removal and destruction of the irritant, and quicker regeneration, than where the vascularity of the part is less—compare the changes in a tendon and its tendon sheath, for example, in a case of suppurative teno-

synovitis; or in the inflamed pericranium and its underlying bone. The rigidity and denseness of the tissue are, indeed, also factors of considerable importance. Thus, an irritant which produces no effect upon the skin, with its thick layer of keratinized epidermic cells, or only a very slight and temporary reaction, may cause a violent inflammation if applied to the conjunctiva. Again, in a compact hard tissue such as bone, great vaso-dilatation and exudation are impossible; while, on the other hand, pain is increased from increased pressure of an exudate, confined by dense unyielding structures, upon the nerve fibres; and the same causes often lead to molar death of the tissue—a necrosis of bone—by interference with its blood-supply. Further, the nature of the tissue may actually lead to the selection and accumulation by it of a particular irritant circulating in the blood. This is most clearly seen in the case of tissues of excretory function, and is exemplified in the action of such bodies as cantharidin and the phenol derivatives, and of bacterial poisons on the kidneys, and more obscurely in the affinity exhibited by tetanus toxin, and by the virus of hydrophobia, for the central nervous system. In these cases it is, apparently, the nature of the tissue which determines local concentration of the irritant, and not the irritant which selects the tissue.

*Position* also exerts an important influence on the character of the inflammatory process. A superficial situation facilitates the removal of the irritant and the discharge of inflammatory products from a free surface; while in body cavities it leads to the accumulation of the exudate outside the tissues involved in inflammation, and not merely in the interstices and spaces of their substance, and thereby it assists the spread of the irritant along the surface in question. The irritant may similarly spread to some extent over a free cutaneous or mucous surface, but here it is not confined as in closed cavities. Skin surfaces are to a large extent protected by their thick and keratinized epithelium against this kind of spread of the irritant; and the same is true in some degree of mucous surfaces, whose epithelium has considerable resisting power, and is in many parts composed of several layers. From a free surface exudation is much more copious than in the deeper tissues—doubtless because there is no tension in the exudate upon an open surface, while in a closed space or abscess cavity increased exudation leads to increased tension, and renders further exudation correspondingly more difficult.

Again, inflammation in the superficial tissues bordering a surface of the body tends to necrosis and the formation of a slough; while in deeper tissues a molecular disintegration of the tissue is more usual. This probably depends upon the fact that a free surface receives its blood-supply from one aspect only, and is therefore more liable to be cut off by the occurrence of stasis and capillary thrombosis. This is exemplified in the occurrence of ulceration

as contrasted with the formation of a typical abscess. Moreover, suppuration occurs more readily in superficial areas, partly again from their relations to the blood-supply, and partly from their liability to extraneous irritation of various kinds. An illustration of this may be found in intestinal tuberculosis, where the mucous membrane exhibits ulceration and suppuration, while there is frequently no evidence of pus formation (and even, perhaps, little caseation) in the infected mesenteric glands of the same region.

The varying *nature of the irritant* at work also introduces marked diversity in the type of inflammation following its action. If the irritant is *non-living*, it cannot give rise to spreading inflammation (in the ordinary meaning of that phrase), and it will usually exert its maximal effect almost immediately upon its entrance into the tissues, since it cannot multiply, or increase its intensity. If it be insoluble, or practically so,its action will be very strictly localized; though if it consist of finely divided particles it may acquire a kind of metastasis, owing to its removal by phagocytes into neighbouring lymphatic glands or other parts. It will produce relatively little injury of tissue, though it may give rise to great capsular production of fibrous tissue. If it be more or less soluble, it will gradually become dissolved and diluted, and will gradually diffuse from the moment of its entrance. Thus, it will sooner or later exert a chemotactic action on the phagocytes, probably leading them to take a share in its eventual removal and destruction.

On the whole, it may be said that non-living irritants (other than very powerful and concentrated poisons) tend to excite productive inflammation. One irritant of a somewhat special character, brought into prominence by a recent addition to diagnostic methods —namely, the X rays—leads us to the borderland which separates inflammatory proliferation from " new growth " in the special sense of neoplasm. Many cases of X-ray dermatitis pass on to a condition of cutaneous epithelioma.

But in the vast majority of cases of inflammation the irritant is an active *living* agent, and usually one of vegetable origin—a bacterium, whose access to the tissues may be primary, though it is frequently secondary to some local injury produced by the action of an inanimate object or external influence (heat, cold, etc.). A good example of the former may be seen in gonorrhœa ; of the latter, in a lymphangitis or a local abscess following a slight wound, or an abrasion of the skin.

*Pus formation*, though in laboratory experiments it can be induced in other ways, is for all practical purposes an evidence of the action of micro-organisms. And though all micro-organisms are theoretically capable of giving rise to suppuration, yet under such conditions as usually obtain in Nature the production of pus is to some extent characteristic of a particular group—the pyogenetic micro-organisms, as they are called—comprising the

*staphylococci*, *streptococcus pyogenes*, *pneumococcus*, *B. coli*, etc. The influence of certain others is to cause leucocytic infiltration without the formation of a definite abscess, implying powerful chemotaxis associated with only a slight degree of destructive action on the leucocytes—such are the *gonococcus*, and the *typhoid bacillus* (in purity). Others, again, including specially the causal agents of *infective granulomata*, are distinguished by a tendency to induce proliferative changes. While a further class leads chiefly to the marked production of fluid exudates, with or without considerable necrosis of tissue—for example, the *Bacillus anthracis*, the streptococci of *erysipelas* and *cellulitis* and the bacillus of *malignant œdema*. With another organism—the *Bacillus aerogenes capsulatus*—gas formation in the substance of the tissues is the salient feature, though probably this is almost entirely a post-mortem event.

The amount of *fibrin* found in exudates, the degree of *digestion* of degenerated cells, the *degeneration* itself, and the *systemic changes* or changes in distant organs of the body, also exhibit striking variation with the varying nature of the irritant concerned. The formation of fibrin in considerable quantity implies a rich exudate and marked leucocytic destruction; its continued presence, a feeble production of digestive enzymes by the irritant. An example of such a condition may frequently be seen in empyema of a pneumococcal origin. Here, in addition to the shaggy layer of fibrin on the pleura, the somewhat thin and watery pus itself often contains large masses and strands of coagulated fibrin.

It is important to observe that the fibrin found upon the surface of an inflamed serous membrane has not necessarily been produced in the fluid effusion within the serous cavity. There is evidence, for example, that in fibrinous pleurisy a considerable amount of fibrin may be formed in the subserous tissue by *coagulation necrosis*—the line representing what was previously the serous endothelium lying over it, or in the midst of the fibrinous mass, and not beneath it, as would be the case were the fibrin merely laid down upon the surface of the pleural membrane. And this is in accord with what we have already said of the tendency to necrosis and the formation of a slough in inflammations occurring in superficial areas.

The *intensity* of irritation is an extremely important cause of variations in the leading characters of the resulting inflammation. By the phrase employed is to be understood, not merely the strength of the irritant, but its strength *relatively* to the resistance of the particular tissue and the particular individual concerned. It impinges, therefore, to a great extent on what we have said of the influence of the nature of the affected tissue. Thus, the streptococcus which is causing erysipelas in a particular subject may, on accidental conveyance to another individual, cause puerperal septicæmia with purulent metritis and septic thrombosis, while it

may give rise merely to a local abscess in the finger of the attendant. And the virus of scarlet fever may, in the individual, not only occasion pharyngitis and an inflammatory eruption on the skin, but also an acute nephritis in the kidney (of different type in different cases), and an inflammatory effusion into joints or suppuration in the middle ear. Indeed, one and the same irritant in varying intensity may give rise to local lesions of every grade of severity conceivable from a mere transient hyperæmia to the most destructive and spreading necrotic inflammation. Nor is this merely a theoretical conception; it actually occurs, as may be gathered from a momentary consideration of the innumerable gradations seen in tuberculous infections, from a mere "dissecting-room nodule" or a "butcher's tubercle" of the skin to the most rapid "galloping consumption."

The *independent* value of *duration* of irritation is exhibited chiefly in relation with inanimate physical and chemical irritants, and determines more especially the extent of the parenchymatous degeneration and inflammatory fibrosis which result. In this respect there is exhibited a similar gradation to that described in relation with intensity of irritation. And that which is in itself only a mild irritant may, by its mere persistence, assume the rôle of an irritant of greater intensity of action. Thus, even a normal physiological stimulus, if sufficiently prolonged or repeated, may become an irritant and lead to the development of inflammation.

In the case of bacterial irritants, their duration of action is so intimately and entirely dependent on their resistance to the defensive processes of the animal body—that is to say, upon their virulence—as to be inseparable in its influence on inflammation from what we have called the *intensity* of irritation and the *nature* of the irritant.

Where the irritation is of low intensity but is long continued, or where a more or less intense irritation and its accompanying acute reaction instead of terminating in the destruction of the irritant and the complete subsidence of the inflammatory phenomena, are succeeded by a persisting irritation of a low grade, a condition known as *chronic* inflammation results.

This condition is marked by the absence to a greater or less extent of all the signs of acute inflammatory reaction, and especially by the slightness of the vascular changes which may be so little marked as almost to appear to be entirely absent. Nevertheless, some degree of passive hyperæmia, at any rate, can usually be detected under these conditions.

The chronic inflammations are either in the main *destructive* in character, and associated with degeneration and death of tissue, as, for example, in very many cases of chronic tuberculosis, or they are of a more *productive* type, and lead to a condition of fibrosis.

## Conclusion.

We must now endeavour, in the light of the information which we have collected touching the various phenomena that may accompany and follow local irritation, and their respective origin and meaning, to find an answer to the question, "What is inflammation?"

The older views as to its nature have been shown to be clearly untenable. Thus, the various theories which have alleged a nervous origin fall to the ground with the recognition of the entirely non-essential nature of the part played by the nervous system even in the vascular changes which in a vascular area accompany the process. The view of Cohnheim and his followers, that the succession of changes witnessed are determined by "molecular alterations" in the vessel walls, fails utterly to afford any explanation of the active emigration of the leucocytes. It is disproved by the repeated observation, that if particular irritants, which on injection into the tissues will occasion violent inflammation, be introduced into the blood-stream, where they can act directly on the vessel walls, no inflammation follows.

The theory of Virchow that the phenomena are those of over-nutrition, due to an attraction of large quantities of nutrient substances, which leads to an abnormal activity of cell proliferation, fails equally to afford a satisfactory elucidation of the events observed. Nor does a condition of over-nutrition ever actually lead to inflammation and the formation of fibrous tissue. Excess of nourishment, whether local or general, is stored away and deposited in the form of fat. And cell growth depends (given adequate nourishment) on quite a different factor—namely, activity exhibited in response to stimulation—and constitutes a self-regulated property of the cell. The point perhaps requires to be emphasized, since there is still a tendency in some directions to regard the rich exudate of inflammation as to some extent determining the productive changes; although, as a matter of fact, the exudation is usually least in evidence where the productive processes are most apparent. If anywhere in the human body a condition of over-nutrition can be recognized, it is surely in the muscles of athletes in training; and, without labouring the point, it may be noted that such muscles undergo hypertrophy and growth of all their constituent elements, not cirrhosis and conversion into cicatricial tissue.

Burdon-Sanderson was the first English writer to mark out a clear path to an adequate conception of the inflammatory process by his strong insistence on its essentially *reactive* nature; and a similar line was followed by Grawitz. Metchnikoff was the first to formulate what may be called the *biological* theory of inflammation; and by his brilliant studies in comparative pathology he demonstrated that the reaction of the phagocytic cells constitutes the most

uniform and the most important feature of the process. Following these lines, we are enabled to exhibit inflammation as a process common to all tissues and to all forms of life under like conditions and similar causation. The evidence of *life* is reaction to stimulation; if the stimulation fall within normal limits, the response is a normal exhibition of activity—a physiological reaction; if it exceeds such limits and becomes excessive, or if it is an abnormal stimulus, the reaction is abnormal and pathological: the stimulus has given rise to irritation, and inflammation is the consequence.

It is sometimes urged that "inflammation" is a clinical term, and as such must be restricted to what was originally intended, or what the clinician now implies by the use of the word; and as a consequence, that it ought only to be applied to conditions seen in vascular animals and in vascular parts. But it need hardly now be pointed out that, as knowledge advances (and indeed if it is to advance at all), no scientific term can permanently retain its original connotation; its content necessarily and unavoidably enlarges. Especially is this the case when it appears that the features or properties most easily recognized, to which in consequence the term was naturally at first applied, are in reality separable accidents of the underlying conditions. It is the thing itself, not the original content of its name, which remains unchanged. And we might as reasonably endeavour to insist that the presence of amber (Greek, *electron*) is essential to the appearance of anything which may properly be termed "electricity," and that in its absence we must not apply that name; or to confine the term "evolution" to its original pre-Darwinian use; or "oxygen" to the acid-forming element, namely, hydrogen. Moreover, it is not a disadvantage to the clinician, but a distinct advantage, to be able to recognize in the inflammations with which he is called upon to deal, not a peculiar and malign condition, which afflicts the higher animals alone, but a beneficent and defensive process—needing at times restraint, at other times active encouragement and exaltation—based upon the fundamental properties of living matter. And, indeed, all modern aseptic surgery, and modern treatment of inflammatory conditions, rests upon the conscious or unconscious acceptation of this view. Any other view of inflammation almost inevitably leads to a false conception of its real nature, and to inconsistent statements and fallacious arguments.

Let it be supposed for an instant that inflammation only occurs in the vascular parts of vascular animals, and that the defensive and reparatory process which occurs under similar conditions in non-vascular animals is not inflammation. What, then, are we to say about those vascular animals whose vascular system is *not* a closed system, but opens into the general body cavity? Are the same processes when occurring in them inflammatory or not inflammatory? The animal is vascular, but the events observed

are identical with those seen in the *avascular* series of animals—which by supposition do not constitute an inflammation—the vascular changes seen in animals with closed vascular systems are entirely absent.

The attempt so frequently made to separate *regenerative changes* from our conception of the inflammatory process leads to an equally unsatisfactory position, and one which cannot logically be maintained. The reaction to irritation may, throughout its course, be *entirely* a process of new formation of tissue ; or it may be exclusively regenerative in a *particular tissue*. The productive changes in the early stages of "stone-mason's lung" cannot be classed as non-inflammatory. Nor can we exclude the earliest stages of a mild tuberculosis—purely productive changes—from the category of inflammatory phenomena. Accordingly, we are compelled to recognize *all* the phenomena which result from irritation, other than the direct and immediate consequences of its action, as integral parts of the inflammatory reaction ; and on the other hand to recognize equally that in the absence or abeyance of one or another of these reactive changes the process still remains an inflammation.

This reaction affords a striking exhibition of that faculty of adaptation to environment on which the persistence of the existing types of living organisms depends. The power of becoming habituated to new conditions, and of retaining the new habits thus acquired, is a fundamental property of living matter. And on it depends the success of the reaction in bacterial inflammations, and the degree of resistance thereafter exhibited to fresh attacks of the same irritant, either in the same region of the body or in other parts.

In his writings on Inflammation, Adami lays down a principle of great importance for the proper apprehension of the relation of normal to abnormal reactive processes in the living organism. It is that "No cell and no tissue is normally in action to the limit of its powers"—that is to say, that "normal stimuli do not induce a maximal reaction." This principle of what Adami has termed *reserve force* explains the observation that the first effect of irritation—by which I mean excessive stimulation, whether it be excessive in duration or degree, or both—is an excess of action, not a defect. The cell is first overworked, later disintegrated. Hence where the action of the irritant is slow enough for us to follow clearly its results, proliferative change is seen to be the first evidence of reaction.

Another principle to which attention must be directed is the law of *over-compensation*, as laid down by Weigert, according to which the tendency of living matter is not merely to compensate, but more than to compensate for katabolic change induced by stimulation. Thus, phagocytes become increasingly phagocytic, and the reaction to bacterial toxins leads to the production of special antitoxic substances in extraordinary excess of the requirement of the moment.

Reviewing the whole question broadly, we are almost irresistibly led to recognize two phases in the inflammatory process: the one directed towards the removal and destruction of the irritant, and thus determining the cessation of irritation; the other directed to the regeneration or replacement of injured tissue, and thus to the restoration of the part to its normal condition. That either of these phases may end in failure, or that the regenerative phase may be carried to excess, is only evidence of the incompleteness of the adaptation yet acquired in the course of a gradually progressing evolution. It must, however, be admitted that there is still very much to be learnt on the question of cell reproduction and the new formation of tissue. And it may be that in the future, when our knowledge is sufficiently advanced, the defensive part of the reaction may alone be recognized as inflammation, *all* new formation of tissue, including both typical and atypical neoplastic growth, falling together under some different term, as exhibiting the different forms of the reaction of regeneration in various kinds of tissue under the influence of various stimuli.

Throughout the foregoing pages the term *irritant* has been constantly employed, and a word must now be said as to what the writer conceives to be the characteristics of an irritant. I take it that an irritant is any agency which is capable of producing injury in living tissue. And I would divide the results of its action into two quite distinct and definite stages: the first consisting of its immediate and direct destructive effects; the second stage reactive, and commencing when and where it ceases to be irritating and becomes merely a stimulus.

To those who would still maintain that regeneration is a *sequel*, and not itself an integral part of inflammation, we may now reply that the same arguments as they employ in the defence of their position might equally be applied to remove the leucocyte reaction also from the category of inflammatory phenomena. This reaction equally witht he reaction of regeneration does not and cannot begin to make its appearance save at the place and at the moment when, either by weakening of the irritant or by the development of adaptation, the *intensity* of irritation (its strength relatively to the resisting power of the cell) has become reduced to a degree at which its action on the cell concerned is no longer irritating and injurious, but merely stimulating. And if the intensity of irritation be on the increase rather than on the wane, both proliferating cells and accumulating leucocytes are eventually alike destroyed, though the precise intensity of action which effects the injury may be very widely different in the two cases, and is, indeed, not necessarily the same for all varieties of the leucocytes themselves.

It is, in fact, only when and where the irritant has become weakened to the level of a timulus—though usually, no doubt, a stimulus both abnormal in character and excessive in degree; yet still

a stimulus, and not a noxa—that the inflammatory reaction to it begins.

Finally, holding as we do that in no case has inflammation been proved to be of nervous origin; and that even were it proved, for example, in the hypnotic phenomena which have been referred to in a previous section, it would merely afford an instance of a *local* irritation or injury produced by excessive and abnormal nervous impulses descending to the part, we may omit any reference to the conception of "subjective injury," and describe the process of inflammation as *the local reaction to local irritation, which tends to the destruction and removal of the irritant, and the repair of the local injury*—or, briefly, *the response to irritation.*

The results of irritation may therefore be conveniently displayed as in the subjoined schema:

- Results of the irritation of tissue
  - 1. Direct action
    - Destruction of tissue.
    - Injury of tissue: degeneration.
  - 2. Reaction = *Inflammation*
    - Defensive phase—leucocytic: chemotaxis, emigration, adaptation, proliferation in leucocyte-forming tissues.
    - Regenerative phase: proliferation and growth of fixed tissue cells, and cells derived from them.

In conclusion it may be said that many of the difficulties which arise in dealing with the subject of inflammation, and all the changes which occur in inflamed areas, would be brought together under one head if it were agreed to employ the term "inflammatory reaction" exclusively to denote the reactive stages, and the term "inflammation" to include the whole of the results of irritation—both its injurious action and the reaction to it. The description and attempted definition given above would then apply to the "inflammatory reaction," and inflammation itself would be described as *the series of changes which occur in irritated tissues both from the action of the irritant and in the course of the reaction to it.* And this accords with the clinical use of the term.

# CHAPTER IV

# INFECTION

By E. W. AINLEY WALKER

In the preceding chapter on Inflammation, it was necessary to refer to the part played by micro-organisms in producing local irritation, and to the differences observed both in the degree and in the salient features of the reaction called forth by different kinds of micro-organisms. To the subject of infection belongs the more particular inquiry into the manner and the results of the attack of living organisms upon the animal body.

Such an attack may remain a purely local phenomenon, or it may become widespread and generalized; and, according to the character of the invading organism and the degree of its activity, it may manifest itself either as an acute or as a chronic process. And just as in the case of inflammation, of whatever origin, it was found that the discussion of the subject involved a consideration, not only of the local irritation and its immediate consequences, but also of the reaction to irritation; so in infection and its complementary phenomenon, immunity, we have to deal first with the special features of the irritation produced by the entrance into the tissues of living organisms, and secondly with the succession of events and changes constituting the response to such invasion. The former involves the consideration of the conditions and the modes of entry and of spread of the invading organisms, and of the immediate and direct effects which they produce upon the animal tissues. The latter is concerned in the main with the phenomena which constitute the reaction to infection, and with the condition acquired in the course of, and, indeed, as the result of, a successful reaction—namely, "acquired" immunity—and forms the subject of the succeeding article.

**Nature of Infection.**—The causal agents of infection belong for the most part to the class of micro-organisms called "bacteria." But besides the bacteria they comprise also certain protozoan and metazoan parasites, to which some attention must be directed at the outset.

The protozoan parasites may, as a matter of convenience, be included for the purposes of our discussion along with the bacteria

under the general heading "micro-organism." They comprise such organisms as, for example, the malarial parasites, trypanosomes, amœbæ, and possibly, in rare cases in Man, coccidia. They are in many respects closely comparable, from the standpoint of infection, with the bacteria, but with this important difference, that, so far as is at present known, they do not in general call forth an immunity reaction, though certainly in the particular case of hæmoglobinuric fever of cattle, which is due to an animal micro-organism, recovery is associated with the development of an immunity.

The majority of the metazoan parasites are either Epizoa or Entozoa, and do not actually penetrate and *infect* the tissues of their host, but merely infest the body surfaces and the canals which open on them. Accordingly, it would appear that they do not produce infection in the strictest meaning of the term. But in this direction the line which separates infection from non-infective conditions cannot be very sharply drawn. In a number of cases we await further information, especially as to the toxic nature or otherwise of the substances which may be elaborated by these organisms, and the extent to which such substances are absorbed by the animal concerned.

Some of the Entozoa, for example, do in fact pierce the superficial tissues of the intestinal wall, and may give rise to definite local lesions, and to this extent they penetrate the actual tissues of their host. Probably, also, they produce noxious substances whose absorption gives rise to systemic disturbance. Undoubtedly the *eosinophilia* which may occur in association with intestinal worms, and notably as shown by Boycott in ankylostomiasis, points strongly in this direction. And although Boycott was himself unable to isolate any toxic substances from the intestinal worms which he investigated, yet others have demonstrated the existence of such substances. If this be admitted, and the production of toxæmia be proved, the condition becomes as truly an infection as if the parasite lay within the substance of the tissues. It is, indeed, exactly comparable to the condition found in cholera, in which the vibriones do not themselves under ordinary circumstances penetrate the intestinal mucous membrane, but exert their action solely through the toxic substances which they elaborate.

Certain other metazoan parasites, such, for example, as the *Trichina spiralis*, various Scolices, Filariæ, *Acarus scabei*, and Chigoe, while actually invading the tissues of their host, and thereby accomplishing a true infection, do not, so far as is known, exert any other than a mechanical action on the invaded tissue, and evoke no reaction other than a local inflammation.

It will readily be understood, from what has thus briefly been indicated, that it is almost an impossibility to formulate a definition of infection of such precision as to at once include all that may

properly be termed " infection," while at the same time excluding all conditions of simple non-infective parasitism.

But it will be sufficient for our present purpose if we consider the term *infection* to denote the entrance of living organisms into the tissues of the animal concerned ; and regard every living organism which makes its way by any means into the substance of another organism, or into a position where its toxic products enter that organism, as thereby infecting it. And in our discussion of the subject we may direct our attention chiefly to the micro-organisms, and especially to bacterial infection, only referring to infection by other organisms where the particular circumstances of the case require it.

Now, if invading micro-organisms are able to live and multiply within the tissues of the animal infected, they produce disease, and such disease is called *infective disease.* To produce disease they must possess the power of living and multiplying in the tissues which they invade ; otherwise they would, under ordinary circumstances, speedily be destroyed. Probably bacteria are continually entering the animal body in small numbers ; and if the observations of Ford, strongly supported as they are by Adami, be accepted, these organisms can be cultivated from the organs of a large percentage of healthy animals. But they do not produce disease at every invasion because their number and virulence are one or both so small that they are rapidly removed and rendered harmless by a mechanism, largely phagocytic, which was referred to in connection with bacterial inflammations, and which will be discussed at length in the article dealing with the problems of immunity.

Infective disease, then, is due to the growth and multiplication, in the body of the animal concerned, of foreign organisms. They produce their effects by elaborating harmful substances which cause local irritation, and, if they reach the blood-stream in sufficient amount, give rise to a condition of intoxication. Micro-organisms may also, theoretically at any rate, produce mechanical effects by rapid multiplication ; but practically the bacteria do not of themselves exert any recognizable mechanical action. Such mechanical effects as do occur in these infections are of an embolic or thrombotic character, and are due directly to the action of larger or smaller masses or particles of blood-clot and fibrin, usually containing colonies of bacteria, and formed as the result of bacterial action on the blood and vascular endothelium. In the case of protozoan micro-organisms the mechanical effects are probably often more important, while the effects of those larger metazoan parasites which make their way into the substance of the tissues of their host appear to be chiefly mechanical, and are for the most part strictly localized.

For many centuries before anything was known of the relation

of micro-organisms to disease, and of the *infective* nature of a wide range of human ailments, it was quite clearly recognized that a number of diseases are *infectious*, or, in common parlance, "*catching*." And the distinction between these characters is of considerable importance in the discussion of infection. It should be clearly understood and carefully maintained. The term *infective* indicates the causation of the disease in question, and is concerned with etiology; the term *infectious* merely denotes ready transmissibility from individual to individual by natural agencies—a property of special interest chiefly from the point of view of sanitary science. And, while we have good reasons for believing that all infectious diseases are infective, there are a number of infective conditions which are not at all infectious.

Infectiousness in disease depends entirely on the fact that in the disease concerned the causal agent is discharged from the body, of the subject in a living and virulent condition. In some cases, however, the infective agent, though alive and virulent at the time of its discharge, is limited in its capacity of carrying on an existence outside the animal body, and dies rapidly when separated from the tissues of its host. In these cases transmission is practically limited to direct transference of the micro-organism by contact of the healthy subject with diseased tissues, or with quite freshly discharged morbid material, as, for example, in the natural transmission of venereal diseases. Diseases of this type, in which the infectiousness depends on contact with a diseased subject, are called *contagious* diseases. To the conditions of contagion and of infection generally we shall return later.

**Infective Micro-Organisms.**—It had long been suspected before the discovery of bacteria, that infection was dependent on the action of particulate and living agents. Their investigation presently threw a flood of light on the hitherto obscure and insoluble problem of the transmission of disease. It was the classical researches of Pasteur which, by establishing (in 1857) the relation of bacteria to putrefactive and fermentative processes, gave a new direction and stimulus to the study of these micro-organisms. But to Davaine belongs the honour of being the earliest observer to establish (in the case of anthrax) the causal agency of bacteria in infection.

Inspired by these discoveries, many observers undertook the investigation of tuberculosis, and a large number of experiments were carried out by the inoculation of tuberculous material in animals. These resulted, after an extended controversy, in the establishment by Cohnheim and Salomonsen, and by Armanni, of the fact that the virus of tuberculosis is capable of growth and increase and spread within the tissues of the animal inoculated, and must be regarded as comparable, for example, with the infective agent proved for anthrax. But its precise character and identity remained undiscovered. About the same time Burdon-Sanderson, a pioneer worker in so many departments of biological investigation, came to the conclusion, from a series

of experiments in which he endeavoured to distinguish between infective and non-infective inflammations, that the degree of infectiveness of an inflammatory condition bears a close relation to the number of micro-organisms present in the lesion, and that wherever metastasis occurs in such infections, micro-organisms are always present in the secondary foci of disease. Three years later, in 1876, he showed that in the case of erysipelas the spreading edge of inflammation always contained large numbers of micrococci arranged in rows, and usually having a crescentic disposition, thus suggesting the name "chaplet coccus" which he applied to them, a name which has since been replaced by the term "streptococcus." Subsequently, in 1881, Ogston determined the constant presence, in a long series of acute abscesses which he examined of a coccus, to which he applied the designation "cluster coccus" (now staphylococcus). Thus, the definite association of particular bacteria with particular diseases began gradually to be established.

It was not, however, until the epoch-making discoveries of Koch had rendered the isolation of bacteria, and their pure culture on artificial media, not merely possible, but a comparatively simple matter, that any great advance could be achieved in pathological bacteriology and in the etiology of infective disease. Since the publication by Koch, in 1882, of the discoveries resulting from his investigation of tuberculosis, of the methods which he elaborated for the growth and identification of the tubercle bacillus, and of the conditions which, as he showed, must be fulfilled before any particular bacillus can be accepted as the proved causal agent of a particular disease, scarcely a quarter of a century has elapsed. But in the interval our knowledge of the relation of bacteria to disease has advanced with rapid strides, and forms to-day a large and continually extending branch of medical science. In more recent years the close investigation of certain diseases prevalent in tropical and subtropical countries has resulted in making us acquainted with a number of disease-producing micro-organisms belonging, not to the vegetable, but to the animal kingdom, and probably their number will receive important additions in the future. But by far the great majority of pathogenetic micro-organisms at present known belong to the vegetable kingdom, and to the group of the Mycetes.

The Mycetes comprise three subgroups—namely, the Hyphomycetes, the Blastomycetes, and the Schizomycetes. Of these, the hyphomycetes, or moulds, which are probably the most primitive forms, possess the most elaborate life-history. Thev exhibit growth in the form of a mycelium bearing hyphæ, by means of which the reproductive functions of the moulds are carried on. But to this class few only of the pathogenetic bacteria belong. Among them may be mentioned the Ray fungus, Actinomyces, various other Streptothriceæ, the fungi of ringworm and of favus, and the *Microsporon furfur*. The Blastomycetes are yeast-like organisms which multiply by budding, new individuals arising as buds thrust out from the periphery of the parent cells. The chief pathogenetic form is the *Saccharomyces mycoderma* (*Oidium*

*albicans*), the torula of thrush, though certain other torulæ have been described as pathogenetic. To the third group, the Schizomycetes, or fission fungi, which form new individuals by simple fission of the parent cell, belong the great majority of the infective micro-organisms.

Though the number of bacteria which, under various conditions, may produce disease, or be associated with morbid processes in different animals, is very considerable, yet the number of those which have been definitely proved to be pathogenetic for man in ordinary circumstances is comparatively limited. Probably in suitable laboratory experiments all, or almost all, bacteria could be made to exercise some pathogenetic action, but those which, under such conditions as ordinarily prevail, commonly produce disease in Man, are probably all included in the table given below, though some authorities might extend it in certain directions:

| | |
|---|---|
| Hyphomycetes: | Achorion Schönleinii. |
| | Microsporon furfur. |
| | Trichophyton tonsurans (numerous varieties). |
| | Actinomyces. |
| | Streptothrix maduræ. |
| | Other pathogenetic Streptothriceæ. |
| Blastomycetes: | Oidium albicans (Saccharomyces mycoderma). |
| Schizomycetes: | Bacillus anthracis. |
| | ,, coli. |
| | ,, diphtheriæ. |
| | ,, dysenteriæ. |
| | ,, enteritidis. |
| | ,, influenzæ. |
| | ,, lepræ. |
| | ,, mallei. |
| | ,, œdematis maligni. |
| | ,, pestis. |
| | ,, pneumoniæ (Friedländer). |
| | ,, pyocyaneus. |
| | ,, tetani. |
| | ,, tuberculosis (mycobacterium). |
| | ,, typhosus. |
| | ,, paratyphosus. |
| | ,, ulceris mollis. |
| | Micrococcus gonorrhœæ. |
| | ,, intracellularis. |
| | ,, pneumoniæ (Fränkel). |
| | ,, melitensis. |
| | Staphylococcus pyogenes (albus, aureus). |
| | Streptococcus pyogenes (erysipelatis). |
| | Vibrio choleræ asiaticæ (spirillum). |
| | Spirillum Obermeieri. |
| | Spirochæta pallida. |

**Factors influencing Transmissibility.**—The description of the particular biological characters and pathogenetic action of these micro-organisms does not fall within the scope of a general discussion

of the phenomena of infection; they are fully dealt with in special works on pathological bacteriology. For our present purpose it is only necessary to recognize that, in their relation to the tissues of living animals, bacteria in general may be divided into the four following classes:

1. Obligatory parasites—bacteria which can only live in living tissues.
2. Facultative saprophytes—naturally parasitic forms which, however, can still continue their existence when discharged from the body.
3. Facultative parasites—bacteria normally saprophytic, but able to live and grow within the body of a living host.
4. Obligatory saprophytes, which *cannot* exist in the tissues of a living animal.

Clearly, the foregoing classification only holds under what may be spoken of as "natural conditions." No hard-and-fast line can in reality be drawn between parasitic and saprophytic micro-organisms. Thus, a bacterium which is usually an obligatory saprophyte, and quite unable to invade the animal body, may, under special circumstances of lowered resistance in the animal to whose tissues it gains access, continue to live and flourish in them, and produce morbid changes, becoming for the time, and for the particular animal concerned, a facultative parasite. Similar results are often readily to be obtained by the methods of laboratory experiment.

On the other hand, the fact that many of the so-called obligatory parasites can be cultivated freely on artificial media under the conditions which can be provided in the laboratory is conclusive evidence that obligatory parasitism is in no way dependent on the fact that animal tissues which form the natural habitat of the bacterium concerned are *living* tissues. It merely indicates the fact that normally a suitable environment, as regards temperature, nutriment, and similar conditions, are only met with in the living body. And there is no reason to doubt that all these micro-organisms will eventually be amenable to laboratory culture.

But although no sharp and final separation can be maintained between the various classes of bacteria indicated, yet under the conditions which govern them and their potential hosts in Nature the distinctions are reasonably well marked, and are of great importance in hygiene and sanitary science. Thus, it is obvious that in diseases due to *obligatory parasites* complete isolation of all infected individuals would instantly put an end to further spread of those infections, and would very shortly annihilate both the diseases and their causal agents.

In the case of *facultative parasites*, on the other hand, little is gained by isolation of the sick. The essential requirement is to

attack the micro-organism in its natural habitat, where otherwise it remains a flourishing saprophyte, prepared at any moment to attack new individuals.

Where disease is due to infection with *facultative saprophytes*, isolation of the sick is very valuable, but it must be associated with the most strenuous application of measures calculated to destroy the micro-organism as it escapes from the body. Otherwise this will take on a saprophytic existence in the external world, and will presently again infect new subjects.

Relations somewhat similar to the foregoing, though not by any means identical with them, hold in the case of many of the pathogenetic animal parasites, in that, while some can exist outside the animal body, others die at once when deprived of the support of living tissues. A number of these organisms, though they cannot grow and multiply outside the animal body, yet leave it in a form in which they can continue an independent existence for a longer or shorter period, as, for example, in the form of ova. Others cannot continue to exist outside the body of an animal, but they can take up their residence in an intermediate host, in which they flourish, and in cases pass particular stages in the cycle of their life-history, as in the case of malarial parasites. In the former case the spread of the disease is best prevented by attacking the infective agent; in the latter it is necessary to destroy the intermediate host either directly or by rendering its natural habitat untenable, a method which has proved peculiarly successful in dealing with mosquitoes in malarial districts.

Diseases due to obligatory parasites can only be spread by direct contact of the animal with infected tissues, and the term *contagious* is applied to such diseases.* Among diseases of this contagious character, those in which the infective agent can directly and immediately infect a healthy individual of the same species may be spoken of as *directly contagious*. But there are others in which the micro-organism does not infect directly, but must first reside for a period in the body of an animal of a different species before it is transmitted to a second individual. In others, again, the infective micro-organism can only be transmitted through the agency of another species, as in some diseases spread by blood-sucking flies. In these cases we may speak of the disease as being *indirectly* or *mediately contagious*. These two classes of contagious diseases may with advantage be termed collectively *directly infectious* diseases, the term *indirectly* or *mediately infectious* being then employed to denote diseases in which the infection is trans-

* Clearly, the term *contagious* must be employed to indicate contact with an infected individual, and not generally of contact with the infective agent, as has sometimes been the practice; otherwise all infective disease is brought within the meaning of the term "contagious," which then ceases to possess any distinctive value.

mitted by means of air and water, or of food and clothing, or by other natural agencies.

| | | |
|---|---|---|
| Infectious diseases | Directly infectious (contagious) | Directly contagious—*e.g.*, syphilis, gonorrhœa. |
| | | Mediately contagious—*e.g.*, malaria. |
| | Mediately infectious | Usually carried by air, water, food, etc.—*e.g.*, typhoid fever, influenza, etc. |

**Predisposition and Insusceptibility.**—During an epidemic of an infectious disease, it may be observed that only a certain number, not in general a very large percentage, of the individuals presumably exposed to infection develop the disease. A number more may experience some slight and transient indisposition, but usually a large proportion fail to exhibit any evidence of infection. Some of these are doubtless persons who have had the disease on a previous occasion, and have become insusceptible; but there remain a number who escape attack who have not acquired their insusceptibility in this manner. Yet of these individuals some may take the disease in a later epidemic, and perhaps even rapidly succumb. Susceptibility is therefore a variable character both in the race and in the individual.

Not only is the predisposition of an animal to infection subject to remarkable variations, but the attacking power or virulence of any given bacterium is itself a variable quantity, and frequently exhibits striking changes. It follows that, besides the bacteria which are clearly recognized as pathogenetic forms, and which commonly give rise to morbid changes, there are a considerable number normally resident upon the body surfaces, and many more existing as saprophytes on dead organic matter, which can upon occasion act as parasites invading the animal body and producing pathological effects. Pathogenicity, in fact, depending as it does upon invasive power, is a function of two variable factors—namely, the virulence of the bacterium and the resisting power of the animal concerned—and hence it is itself a variable quantity.

The variability of bacterial virulence is a feature of great importance, but the conditions on which it depends have not by any means been fully elucidated. It is, however, amenable in a high degree to influences precisely similar to those which modify and govern the resistance of the animal body to infection. Thus, it may be attenuated by unfavourable conditions of temperature, nutrition, moisture, and the like, and is heightened by successful invasion of the animal body. The resistance of an animal—or, more properly, its *relative* resistance to any particular bacterium of given virulence—is similarly dependent on a variety of factors, such as species, age, condition, and nourishment, and it is found to be increased in a special manner for a longer or shorter period following successful

reaction to a previous infection by the particular bacterium in question.

Detailed experiments by many observers have demonstrated the effect of hunger and thirst, improper food, fatigue, extremes of temperature and humidity, loss of blood, and shock from any cause, in lowering the resistance of an animal. On the other hand, its resistance is readily increased—apart from any specific method of treatment—by all that makes for its general well-being.

Hence it is necessary to recognize clearly that the terms *predisposition* and *susceptibility* are purely relative, and that the conditions which they indicate are subject to considerable variations both in the individual and in the species. Probably neither absolute susceptibility nor absolute insusceptibility is anywhere existent. Yet there are some cases where, under natural conditions, a close approximation to such a state appears to obtain. Thus, for example, as Metchnikoff asserts, no amount of tetanus toxin is sufficient to kill a scorpion, so great is its resistance to this poison ; while, on the other hand, the mouse is so susceptible to the invasion of anthrax that even if the lower part of the tail be amputated within one minute of the inoculation of its tip with anthrax, the animal nevertheless, succumbs to the infection.

The degree of predisposition or of insusceptibility naturally possessed by an individual or species is evidently a matter of heredity. There is, however, no evidence to show that individually *acquired* predisposition or insusceptibility is transmissible, any more than is the case with other acquired characters. On the contrary, the experiments of Bulloch and other observers tend to show that acquired resistance is not transmitted in the germ plasm ; while the increased resistance of sucklings, due to their absorption of protective substances eliminated in the mother's milk, is only a passive and temporary phenomenon.

The development of increased resistance in a race or species may perhaps be explained in different cases in one or other of the following ways : It may be due to the appearance of accidental variations in the direction of diminished susceptibility, which, being favourable to the persistence of the species, tend to be preserved and gradually increased in the process of adaptation to environment. Or it may be due to gradual elimination of the more susceptible members of the species by the disease in question. These individuals tend to succumb to the disease and leave no progeny, while the less susceptible members of the species survive and transmit their relative insusceptibility. And probably both these factors play a part. But, as might be expected, evidence is lacking that they are in action in all cases. In a number of infections resistance has not perceptibly increased in many centuries. If the forces in question are actually at work in the cases referred to, their effects are, at any rate, not at present recognizable ; and we have, indeed,

no means of estimating the length of time that may be needed in particular instances to yield visible effects. In the case of plague, for example, the susceptibility of certain races appears to have undergone no diminution during historic time. It must be remembered, also, that since the dawn of rational therapeutics the natural tendency of disease to eliminate the more susceptible individuals and races has been steadily opposed by artificial measures (medical treatment) directed to their cure and preservation.

**Paths of Infection and Modes of Spread of the Infective Agents.**—Probably all infections, excepting those in which the infective agent is introduced directly into the circulating blood, begin exclusively as local processes; and they occasion the development of local inflammation. If they spread throughout the body from their original site, they are usually accompanied in their course by the formation of inflammatory foci in the various situations where the infective agent gains new foothold. Thus, even the exanthemata, which very rapidly become generalized, appear to commence in local inflammations affecting the respiratory tract, and, as their name implies, their generalization is accompanied by cutaneous eruptions which are of an inflammatory character.

The path of invasion in specific infections is usually by the mucous surfaces, respiratory, alimentary, or urinary, respectively, save in the case of the "fly inoculations" (*e.g.*, malaria, yellow fever, and trypanosomiasis), where the micro-organisms are introduced directly into blood-capillaries; syphilis, which usually enters at a slight abrasion of the surface; plague, which apparently may be either a flea inoculation, or an infection through the respiratory mucosa, or through abrasions of the skin, especially among barefooted peoples; tetanus and hydrophobia, which are wound infections; and anthrax and glanders, which in Man are also usually cutaneous infections. Pyogenetic micro-organisms, on the other hand, commonly gain access to the tissues through a wounded surface.

Whether bacteria can enter the body through an unbroken surface is still in doubt; certainly they can make their way into the tissues from hair follicles and sebaceous glands, and thus set up a local inflammation and infection. And it is at least possible that, where vapours, fluids, and even finely divided metals, can be to some extent absorbed, bacteria may also be able to gain entrance. But doubtless in the vast majority of cases, at any rate, some local injury or lowering of resistance, as, for example, by unusual cold or heat and the like, is a determining factor in bacterial invasion. It must not be forgotten, however, that micro-organisms may actually be carried into the tissues from a superficial area by phagocytes which have ingested them without succeeding in accomplishing their destruction.

After the infective agent has acquired a local foothold in the body,

phagocytic cells may also play a part in its dissemination. Evidence of this is found in the frequency with which lymphatic glands exhibit the first signs of the spread of an infection, and in many cases form the seat of secondary abscesses. But the commonest, as it is the primary, mode of spread is undoubtedly by continuity of tissue, whether along the lymphatic spaces and canals which permeate its substance, or over a free mucous surface of the body. Discontinuous spread by dissemination is fortunately a less usual event, and is in general a secondary phenomenon.

The spread of infection along a mucous surface is, naturally, most rapid in the normal direction of flow along it, while it is to some extent retarded in the reverse direction. Thus, for example, tuberculosis of the kidney frequently results in secondary tuberculous infection of the bladder, but the converse is rare; nevertheless, a purulent cystitis often leads eventually to septic nephritis by spread of the infection against the direction of urinary flow.

Other modes of spread which sufficiently explain themselves are by ulceration or rupture of an abscess into a hollow organ, body cavity, vein, duct, or lymphatic channel; or, in the case of the nervous system, by invasion of the cranial cavity and cerebrospinal fluid, as, for example, from the nasal mucous membrane, and possibly in other cases by transmission along the perineural lymphatic sheaths to the central nervous system and its coverings.

If the infective agent reaches the lymphatic circulation, and especially if it passes onwards into the blood-stream, it tends to become disseminated widely, and unless it is speedily destroyed by the protective mechanisms may give rise to general infection of the body. It may, however, be arrested temporarily or permanently in the lymphatic glands, its further progress being checked by the phagocytic activity of leucocytes, and the succeeding events in the gland being those of localized bacterial infection. In such a case the lymphatic path along which the bacteria have travelled may or may not afford evidence of infection or of toxic irritation, according to the number and virulence of the micro-organisms present, and the activity of their toxic products.

Where bacteria gain access to the general circulation, the subsequent course of the infection depends in great measure on the manner of their liberation into the blood, and on their number, rapidity of growth, and virulence, relatively to the protective and resisting power of the blood and tissues.

In the first place, dissemination may occur, not by the escape of free bacteria into the blood-stream, but by the detachment of fragments of clot and fibrin from a septic thrombus. Thrombi of this nature are frequently formed in veins in areas of acute bacterial inflammation, as explained in the discussion of that subject. Colonies of bacteria multiply in their substance, and where the action of the micro-organisms causes softening and degeneration

of the clot, fragments are readily detached and carried by the circulation to distant organs, where they form septic emboli in the arterioles. Thrombosis occurs around the emboli, and secondary foci of infection are thus set up, which, more especially in the case of the pyogenetic cocci, frequently go on to the formation of metastatic abscesses. Such a condition, unless extremely limited in duration and extent, is likely to terminate in septicæmia and pyæmia.

On the other hand, where *free* bacteria gain access to the blood, a condition of bacteriæmia is produced. And if the bacteria persist and multiply in the blood-stream, the condition is spoken of as one of septicæmia, in contradistinction to the sapræmia (toxæmia) produced by the presence in the blood of absorbed toxic substances which have been elaborated by still localized micro-organisms. But it must be clearly understood that the dissemination of the infective agent by the blood-stream does not necessarily entail the existence of a condition of septicæmia in the usual acceptation of that term. Even in a strictly pathological sense, the term is regarded as implying the definite establishment and multiplication of micro-organisms in the blood, not their mere passage through it; while in its narrower clinical usage it is practically confined to cases of invasion of the blood by pyogenetic micro-organisms.

The results which follow the escape of bacteria into the blood may, in fact, be conveniently considered under the three following categories:

1. The bacteria which gain the blood-stream are *incapable* of surviving in it, and are rapidly destroyed. Here the infective condition remains localized, and only spreads, if at all, by continuity of tissue. Such general disturbances as may be associated with the condition are due entirely to the absorption and diffusion of toxic substances produced locally—as, for example, in diphtheria and tetanus. Probably in every infection some bacteria escape into the blood; in the majority of cases, however, they rapidly succumb to the antibacterial properties of this fluid.

2. The bacteria are able to *persist* in the blood for a certain time. Here throughout the greater part of the duration of the disease there are probably always some living and virulent bacteria in the blood-stream. These are carried throughout the body in the circulation, and frequently gain a local foothold in various distant parts, thus leading to the establishment of secondary foci of infection. This is doubtless the case in all the exanthemata, and in the other infections, whether acute or chronic, in which any evidence of metastasis appears. In the more chronic infections the number of living bacteria in the blood at any moment is probably very small, and their ability to maintain themselves in it is very limited, so that secondary foci are only established slowly, and are relatively

few—as, for example, in chronic tuberculosis spreading by the blood; but in acute conditions the number of micro-organisms actually present in the blood is probably greater than has usually been supposed. Thus, in the case of typhoid fever, it has been found, that when the Gruber-Durham (so-called Widal) reaction fails to give conclusive results, a confirmatory diagnosis can be made from the blood, comparatively small quantities of which, when suitably inoculated, yield pure cultures of the typhoid bacillus.

3. In the third case which requires consideration the bacteria become *established* in the blood, and there grow and multiply. The condition is now to be spoken of as "septicæmia." It is most readily recognized in cases of infection with the pyogenetic micro-organisms. In these cases it frequently results in the formation of multiple pyæmic abscesses in various organs where metastatic foci of infection are established. The disease is then spoken of as "pyæmia," and is commonly, though not invariably, associated with a high degree of leucocytosis, whence the name originated. Some of the specific infections also appear to be definitely septicæmic in character, notably Malta fever, malaria, and certain cases of plague; and probably in very many a fatal termination is preceded by a septicæmic stage—as, for example, in acute general tuberculosis or in anthrax.

The formation of secondary foci of infection, or metastasis, which occurs (apart from the production of septic embolisms already described) when free bacteria *persist* in the blood-stream, is probably attributable to the action of the vascular endothelium. This endothelium, as has already been explained in the article on Inflammation, possesses phagocytic properties, and can take up bacteria circulating in the blood. The bacteria thus ingested may survive and multiply within the endothelial cells, and thus form new centres of infection, starting from the endothelium of the vessel walls.

**The Mode of Action of Infective Agents.**—Infective agents act upon the tissues which they invade either directly by the mechanical effects of their increase and growth, or indirectly by means of chemical substances which they elaborate in the course of their metabolism. But, except as regards the production of thrombosis and infective embolisms, mechanical action is in the main confined to infection with the larger animal parasites.

The pressure and irritation which these larger parasites occasion lead to a local inflammation, which usually results in capsular fibrosis, such as is seen around hydatids and trichinæ, except in cases where the condition is complicated by bacterial invasion. On the other hand, where the animal parasite is accompanied in its invasion by bacteria, or becomes secondarily associated with them, suppuration is a common sequel of the infection. This is attributable chiefly to the bacterial action—that is to say, to the production of chemical irritants.

The chemical substances which bacteria produce are very numerous, and many of them exert a highly irritating action on the tissues. By far the most important of these bodies are the so-called "toxins." These are the specific poisons of bacteria, and they are divided broadly into intracellular and extracellular varieties. Toxins which appear in the culture media in which bacteria are grown are spoken of as "extracellular" toxins, while those which are found within the bodies of the bacteria themselves are termed "intracellular." The latter only become extracellular either by a process of bacterial excretion or by the death and dissolution of the bacteria themselves. Probably in a majority of cases the so-called "extracellular toxins" are primarily of intrabacterial origin, but possibly in some cases they are produced externally by the action of ferments formed, and excreted into the surrounding medium, by the bacteria. This seems to follow from the fact that in certain cases the culture media may be highly toxic, while the washed bacterial bodies filtered off from the media may be almost entirely lacking in toxicity.

Besides their toxins, the bacteria produce various other substances, such as gases, pigments, acids of the fatty and oxy-acid series and their amides, alkalies, bodies of the aromatic series, albumoses, peptones, and enzymes. Some account of these substances is to be found in the textbooks of bacteriology, and the majority of them need not detain us here, though possibly some of them possess a greater importance in infection than is usually admitted.

The action of bacterial enzymes is to cause the digestion and solution of the tissues which they attack, and in the process they lead to the production of some at least of the noxious substances elaborated in the course of an infection. In the case of diphtheria, for example, an enzyme secreted by the bacilli has been found in "diphtheritic membrane" both by Roux and Yersin, and by Sidney Martin. And Martin regards this enzyme as constituting the true diphtheria toxin, which forms toxic albumoses (the actual poisons of diphtheria) by its digestive action on the tissues in the local lesion.

The interest and importance of toxic albumoses is very considerable, since it appears that poisonous substances belonging to the albumoses (or occurring in close combination or association with albumoses) are numerous and widely distributed in Nature. Thus, abrin (the poison of jequirity-seeds) and ricin appear to exhibit the reactions of albumose, so also do the toxins of snake-venoms, and various fever-producing albumoses have been isolated from bacterial cultures.

Whether the true bacterial toxins are in general albumoses, or simply bodies of unknown constitution which occur in close association with these albumoses or actually linked to them, and in consequence precipitated with them from solution by the reagents commonly employed, remains an open question. Possibly they are not themselves albuminous in nature, since it was demonstrated both by Buchner and Uschinsky that the bacteria which they investigated could still form their usual toxins when grown in culture media from which all traces of albuminous matter were carefully excluded. Moreover, Brieger and Boer succeeded in preparing the toxins of diphtheria and tetanus in a form in which they yielded no protein reactions at all, even after considerable concentration of the solutions.

**The Effects of the Action of Infective Agents.**—The effect of the action of infective agents is to produce irritation of the tissues at the site of their activity, and, while this irritation may in certain cases be purely mechanical in character, it is in the majority of instances of chemical origin. At other times both forms of irritant action may be in evidence—as, for example, in the case of infective embolisms.

At the point where the infective agent first gains foothold in the tissues there is set up a centre of local irritation, and similar centres of irritation are developed in the course of the disease wherever the invading organism becomes localized in metastatic foci of infection. Secondary areas of irritation may also arise, without metastasis of the micro-organisms themselves, as the result of the action of their toxic products in parts or organs where these substances tend to accumulate in considerable concentration—as, for example, in the kidney in the course of their excretion. This condition is well exemplified in the diffuse parenchymatous nephritis which may occur in diphtheria and various other specific fevers. Thus, while the first result of an infection is the production of a local lesion, following on this primary effect there ensue a series of general disturbances throughout the body, which are occasioned either by the absorption and diffusion of toxins from the original area of infection, or by the dissemination of the micro-organisms themselves and the production of toxins in a number of scattered foci, and it may be even in the blood itself. Accordingly, the results of an infection may be divided into *local* and *general* effects.

The local action of infective micro-organisms, whether in the primary focus of infection or in the secondary foci which arise as the result of dissemination and metastasis, is to occasion tissue injury, followed by inflammatory reaction. These effects have already been discussed in the article on Inflammation. The degenerative changes in the affected tissues, the vascular phenomena, the leucocyte reaction, and the regenerative process, occur precisely in the manner there described, where it was noted further in anticipation that infection constitutes by far the most common cause of inflammation.

The general and systemic disturbances resulting from infection may be summed up briefly under the term "intoxication" (or toxæmia) and its effects. They comprise blood-changes, tissue degenerations, pyrexia, and disordered metabolism.

Of the *blood-changes*, by far the most important are those which concern the leucocytes and leucocyte-forming tissues. These will most suitably be dealt with in the discussion of Immunity, and nothing further need be added here to what was said upon this subject in speaking of the general leucocyte reaction in inflammation, beyond the fact that there is evidence of increased activity in the bone marrow, the spleen, and the lymphatic glands in general.

In an acute infection of some duration and severity, the pale fatty marrow of the shafts of the long bones may become entirely converted into the pink variety under the stimulating action of bacterial products. Under similar conditions, as well as in continued chronic inflammations, the lymphatic glands and spleen always exhibit a more or less marked enlargement. This may be due in part to increased activity of lymphocyte formation; it is also due to the determination to these situations of phagocytes which have ingested particles of degenerated tissue, dead leucocytes or other cells, or micro-organisms, apart from swelling and enlargement caused by actual inflammation of the glands consequent on infection by disseminated micro-organisms. Frequently the enlarged glands are readily palpable in superficial situations, as is the case, for example, in various exanthemata and in the secondary stage of syphilis, or the spleen itself may be distinctly felt, as in enteric fever and most remarkably in malaria. In the more chronic infections, particularly those which lead to productive changes with or without subsequent degeneration of the new-formed tissue, the glandular enlargement may be very marked.

The total acids of the blood are frequently increased in quantity, and the presence of abnormal acids, such as lactic acid, has been described. In other cases observers have found increased alkalinity, especially at the onset of infective illnesses. The coagulability of the blood may also be either increased or diminished, and this is probably, to some extent at least, dependent on the degree of leucocytosis or leucocytopenia existing.

Anæmia and oligocythæmia occur, and may reach a high degree, though the poverty in red corpuscles may be masked in the blood-count to a greater or less extent by an accompanying concentration of the blood due to a condition of hypoplasmia (*vide* Inflammation). In many infections the destruction of red corpuscles is probably due in part at least to the action of hæmolysins of bacterial origin. The hæmoglobin thus set free into the plasma may cause a staining of the vascular endothelium, such as is frequently seen in subjects who have died of septicæmia.

Multiple small hæmorrhages may also occur in infection, either by diapedesis through unbroken endothelium, or following on degeneration and rupture of capillary walls, with the production of petechiæ and ecchymoses.

Of the *degenerative changes* associated with infection, cloudy swelling (or albuminoid degeneration) is by far the most common, and probably occurs in some degree in all infections of sufficient severity to produce symptoms of general disturbance. It is followed, if the infection be persistent, by fatty changes in the affected tissues, the organs usually first affected being the liver, the kidneys, and the heart.

In the more chronic infections various other degenerations, and notably amyloid degeneration, frequently make their appearance at a later stage, as was noted in the discussion of Inflammation.

*Fever* is a usual feature of all infective disease other than the slightest and most transitory local lesions. It is in general accompanied by pyrexia, though in certain stages or in certain cases the

temperature may even be subnormal. This pyrexia and the metabolic disturbances of infection, which together constitute the process known as "fever," are discussed in the article devoted to that subject. Symptoms either of nervous irritation or paralysis also occur in many of the infections. These, save for such specific toxic effects as are associated with diphtheria, tetanus, and hydrophobia, for example, may be regarded as an integral part of the febrile process, and the functional changes which occur in the skin, the heart-beat, respiration, and the urinary excretion, are also most conveniently dealt with in the same connection.

**Specificity in Infective Disease.** — When an infective disease presents characters which clearly distinguish it from all other known diseases, and is invariably associated with the presence of a particular micro-organism, which gives rise to that particular disease in the species of animal concerned, and to no other, the disease in question is said to be *specific*, and the infective agent which produces it is spoken of as the specific causal agent of the disease.

The conditions which must be fulfilled before specificity can be established in the case of any given micro-organism were originally laid down by Koch in the form of his familiar "postulates." These are now usually stated in the following somewhat modified form:

1. The particular micro-organism in question, and no other, must invariably be present in typical lesions of the disease concerned, and in no other disease.
2. When transferred under suitable conditions to healthy individuals of a susceptible species, the micro-organism must produce the disease in them, and must be recoverable from their tissues in an active condition.
3. If capable of artificial cultivation, the organism must produce the same disease when inoculated from cultures into healthy animals, and it must be again recoverable in pure culture from their tissues.

The foregoing conditions suffice to establish what may be called the *biological* specificity of a disease. To them a fourth may be added, which will establish the *chemical* specificity of the phenomena concerned, namely:

4. The toxic substances obtainable from artificial cultures of the infective agent (whether present in the culture media or confined within the bodies of the micro-organisms themselves) must be in chemical and physiological agreement with those found present in the tissues of affected animals.

Chemical specificity has at present been demonstrated only in the case of *diphtheria*, *tetanus*, and *anthrax* (Sidney Martin); but biological specificity has been definitely proved, not only in those diseases, but also in the case of *actinomycosis*, *glanders*, *gonorrhœa*, *Malta fever*, *malignant œdema*, *plague*, *syphilis*, and *tuberculosis*. Several authors also claim successful animal experiments with

the *Bacillus typhosus* as the causal agent of specific *typhoid* lesions.

In *epidemic cerebrospinal meningitis*, *influenza*, *kala-azar*, and *Madura disease*, only the successful animal experiment is lacking; while in *malaria*, *relapsing fever*, *sleeping sickness*, and *yellow fever*, artificial cultivation of the causal agent is alone at fault. Both in malaria and in yellow fever the disease has been experimentally transmitted by the agency of blood-sucking flies (Anopheles and Culex); in sleeping sickness transmission from the rat to man has taken place through a cutaneous abrasion; in relapsing fever the disease has been conveyed to monkeys by inoculating them with blood taken from diseased subjects; in kala-azar the flagellate stage of the organism has been cultivated by Roger, and the transmission of the infection has been traced by Patten in India to the bed-bug. As regards syphilis the condition has been transmitted to anthropoid apes by subcutaneous inoculation of syphilitic material obtained from man, and the *Spirochæta pallida* has been detected in the resulting lesions. Further, this organism has recently been cultivated by Noguchi.

In a similar degree the specificity of *favus*, *pityriasis versicolor*, *scabies*, *ringworm*, and the infections with the larger *animal parasites*, has been made reasonably certain, though in these cases all the conditions laid down by Koch have not been altogether fully satisfied. And it should be mentioned that in ringworm somewhat numerous different varieties of Trichophyta and Microspora are found in different cases of the disease.

Finally, in *leprosy* only the constant presence of a particular micro-organism has been proved, since both inoculation experiments in animals and all attempts at artificial cultivation of the bacillus have been hitherto entirely unsuccessful.

In the following diseases there is more or less abundant and conclusive evidence of infective origin, though their specific micro-organisms are either still unknown or fail of general acceptation:

| | |
|---|---|
| Acute rheumatism (in all its manifestat ions). | Rubella. |
| Coryza. | Scarlatina. |
| Morbilli. | Typhus. |
| Mumps. | Varicella. |
| Pertussis. | Variola. |
| Rabies. | Vaccinia. |

A micrococcus has been described by Buzzard in *Landry's paralysis*, and demonstrated in the spinal membranes, while *acute anterior poliomyelitis* may be mentioned among diseases probably also of infective origin.

**Symbiosis in Relation to Infection.**—Symbiosis is a not infrequent phenomenon in Nature, and it occurs in a considerable proportion of infective conditions; but the extent and direction in which it

affects the course and character of these infections has been as yet but little ascertained. Undoubtedly it plays an important part in the normal history of various plants and in a number of fermentative processes, and possibly it exerts a helpful influence in the process of digestion in animals. The digestion of cellulose, for example, has been attributed in part, at any rate, to bacterial action. Certainly in leguminous plants the symbiotic growth of nitrifying organisms upon their roots is of a very definite nutritional value, and it has been clearly shown that plants in general cannot thrive when grown in sterile nutritive materials.

Of the effect of the symbiosis of bacteria on their mutual activity little is known save in a few particular instances. The changes concerned in the ripening of various kinds of cheese, and the production of koumiss by the fermentation of mare's milk, as carried on in the Caucasus, are brought about by the co-operation of two or more symbiotic micro-organisms. Similarly, in the case of tetanus infection, the presence of symbiotic aerobic micro-organisms, which rapidly use up the supply of oxygen present in the tissues, appears to be essential to the growth and toxin production of the *Bacillus tetani*, which is an anaerobic organism. In the case of diphtheria, again, the disease is found to be in general of a greater severity when streptococci are also present in the local lesion. Whether this is due merely to an increased lowering of tissue resistance as the result of the double infection, or to a definitely favourable influence of the symbiosis on the activity and toxin production of the diphtheria bacillus, is not certainly known, but it is maintained by competent observers that toxic paralyses occur with greater frequency after such infection than in the cases where the diphtheria bacillus alone is present. In tuberculosis of the lungs, to take another example, much of the suppuration and breaking down of tissue is undoubtedly attributable to the results of secondary infection of the affected parts with pyogenetic micro-organisms.

In laboratory experiments it is a familiar fact, established by very numerous observations, that the result of symbiosis may be an alteration either in the direction of increase or diminution of the virulence and activity of particular micro-organisms, and we may probably conclude that it exerts an influence of considerable importance in many infections. Especially is this the case in the majority of wound infections, and perhaps also in a large proportion of acute infections of the urinary and alimentary tracts. In typhoid fever and cholera, for example, there is reason for believing that the morbid changes which occur are not entirely due to the activity of the specific micro-organisms of these diseases, but depend in part on an increased activity and virulence of other organisms present in the alimentary canal.

In such cases it may be that one organism produces substances

which are favourable to the growth and the toxin formation of the other, or the micro-organisms may actually co-operate in the elaboration of particular poisons which neither of them alone is able to produce. Thus, Kohlbrugge isolated from a case of diarrhœa a bacillus and a spirillum which in symbiosis produced a peptonizing ferment. Neither of these organisms could form the ferment in the absence of the other, and after they had been cultivated separately for a time they were found to have entirely lost the power of forming it even when again united in symbiosis.

**Latency, Incubation, Recovery, and Relapse**—*Latency.*—Although the usual sequence of invasion of the body by bacteria is either the prompt destruction of the micro-organisms by the reactive and defensive mechanisms of the animal, or the production of evident disease, it is undoubtedly the case that on occasion a third alternative presents itself, and neither of these results occurs, the micro-organisms remaining in the tissues alive and virulent, but in a *latent* and inactive condition. The infection persists without producing any of the manifestations of disease.

True latency is not merely an unusually slow development of the disease in any ordinary meaning of that phrase, for its duration may be greatly in excess of anything that could reasonably be attributed to such a cause. Thus, in a case recorded by Abraham, leprosy developed in an individual no less than forty years after his last possible contact with the infection. The condition is, in fact, apparently one in which the resisting power of the animal and the virulence of the micro-organism exactly balance one another, so that a state of equilibrium is reached between the forces tending to the production of irritation and injury of tissue and those tending to the destruction of the invading organisms and repair.

The existence of an antecedent condition of latency is clearly very difficult to prove in any particular case, on account of the difficulty of excluding the possibility of a recent unrecognized infection shortly preceding the development of the disease. But, besides the case of leprosy referred to, cases have been recorded both in syphilis and tuberculosis in which latency of the infective agent seemed to afford much the most probable explanation of the eventual development of the disease in question. And this is precisely what might *a priori* be expected to occur, even if but rarely, in a certain number of cases of infection, since in every infection there is necessarily a contest between two opposing mechanisms or tendencies—the one bacterial, tending to produce disease; the other defensive and regenerative, tending to destroy the invading organisms and repair the injury produced.

Frequently the bacteria gain the upper hand (temporarily or permanently), and the disease becomes manifest; but still more frequently the reaction of the animal body is so successful and complete that no perceptible symptoms are declared. Between

these two extremes will lie the cases where a more or less enduring equilibrium is established between the attacking and defending forces. And probably a temporary equilibrium of this character occurs more frequently than is usually suspected, especially in the naturally more chronic infections like tuberculosis. A parallel condition of approximate equilibrium is seen in cases where disease is fully manifest, but shows no tendency either to advance or recede —as, for example, is at times the case in persistent indolent ulcers, old abscess cavities, and sinuses remaining after operations, where after-healing can only be induced by deliberately exciting a more violent inflammatory reaction.

From these considerations it would naturally follow that, where infection is latent, any significant increase in the reactive and resisting power of the animal concerned must result in rapidly terminating the infection by leading to the destruction of the "latent" micro-organisms, while any change which lowers vitality and adversely affects the general well-being of the animal will favour an increased activity of the infective agents, and will probably determine the development of visible disease. In this connection it is worthy of note how frequently the development of tuberculosis, for example, or the recrudescence of the signs of active syphilis, follow the subjection of the individual concerned to such depressing conditions as insufficient nourishment, overwork, the indulgence in various excesses, and the like.

*Incubation.*—Between the moment of infection and the exhibition of appreciable results of the microbic invasion a definite interval necessarily elapses. This interval is spoken of as the "incubation period" of the disease concerned, and in a number of infective diseases it has an ascertained and fairly constant length.

As has already been stated, the great majority of known infective agents exert their pathogenetic effects by means of toxins which produce conditions of local irritation and general toxæmia. But the amount of toxin which gains entrance to the body of an infected animal at the moment of infection is usually, and apart from laboratory experiments, quite unimportant. And since with all varieties of toxins there is (for each particular animal) a definite minimal dose, quantities less than which are insufficient to induce disease, it follows that a certain interval of time—dependent on the virulence of the organism, the resistance of the tissues, and other circumstances which may affect the production of toxins by the infective agent—necessarily intervenes between infection and the development of recognizable morbid changes in the animal concerned.

In addition to the primary incubation period, it is found that in a number of infections there occurs, after the lapse of a further interval of time (often, again, of fairly constant length), evidence of dissemination and of the formation of secondary foci of infection,

manifesting itself in the development of inflammatory cutaneous eruptions and the like. In other infections no such secondary manifestations appear, and in some at least of these it is unquestionably the case that the infective agent does not in general penetrate beyond the primary lesion, but remains strictly localized, producing general effects only in proportion to the absorption and diffusion of the toxins formed in the primary focus of infection—as, for example, in diphtheria and tetanus.

*Recovery.*—But little need be said at the present juncture on the subject of recovery from infective disease, since almost all that has been clearly ascertained concerns the subject of Immunity, and will be fully dealt with in that connection.

In by far the greater number of infections of bacterial origin—and these form a vast majority of all infections—there is a definite tendency to recovery. Convalescence and not death is the common sequel of infectious disease, and of a large proportion of all other infective conditions. And just as in conditions of *inflammation* the local irritation stimulates the reactive processes which tend to the removal and destruction of the irritant, and the restoration of the affected tissues, so in *infection* the general irritation produced by the bacterial toxins leads to a general reaction of the organism, which not only tends to the removal and destruction of the irritant (and the micro-organisms which are forming it), but also to the development of increased resistance against the attack of the bacteria in question. The investigation of the intimate nature of this reaction, which leads to the elaboration of specific antibodies and lysins endowed with the property of entirely arresting the toxic action of bacterial products, and of destroying and dissolving the bacteria themselves, forms the special sphere of the science of immunology.

In the case of infection with the animal organisms there is, however, no evidence of any immunity reaction; indeed, in the opinion of the majority of those who are most conversant with these particular diseases, the evidence points in a contrary direction. Hence, any existing degree of immunity in particular races would seem to be referable rather to survival of the fittest and the preservation of accidental favourable variations in past generations than to acquired characters of the individuals themselves. Yet recovery may occur—as in malaria—by the organism eventually dying out or being destroyed by suitable drug treatment.

In certain of these infections there is apparently no tendency whatever to recovery under natural conditions. Recovery may, indeed, occur owing to the death of the infective agent, but there is no mechanism for its destruction or removal. Thus, hydatids and the cysts of *Trichina spiralis* become shut in and enclosed by capsular fibrosis, but they are not killed, and they do not necessarily die within the capsule. And in the case of prehensile intes-

tinal worms (if their invasion be indeed regarded as an infection), there is no natural means by which the host can terminate the invasion.

*Relapse.*—A relapse—in the proper scientific meaning of the term—is said to occur when convalescence from an infective disease is suddenly interrupted by a fresh attack of the same disease. Malta fever normally affords an example of the condition, but the most striking examples are seen in typhoid fever, where typical relapses occur in a fair proportion (3 to 10 per cent.) of cases.

The term may also be applied to the successive cycles of malaria and relapsing fever. In these examples it has been quite clearly ascertained that each relapse coincides with the reappearance in the circulating blood of *free* sporocytes of the malarial organism, or of the spirillum of Obermeyer, respectively. Each relapse is obviously a reinfection from within, and in malaria its origin is easily comprehensible, depending as it does on a definite event in the life-history of the asexual cycle of the parasite. In relapsing fever, however, it is not at present at all evident how either the disappearance of the spirilla from the general circulation, or their later reappearance in it is brought about.

The problem of the relapses of typhoid fever is equally unsolved. Typhoid relapses occur at a period when considerable immunity has been developed, so that the toxins of the bacillus have been neutralized and the micro-organisms themselves in greater part destroyed. How, then, does it come about that the bacilli begin to multiply again, exhibiting renewed activity and forming fresh toxic substances?

It has been shown that typhoid bacilli invade the gall-bladder, and there multiply, and the suggestion has been made that in certain cases the cystic duct becomes occluded for a time by an inflammatory swelling of its mucous membrane, thus shutting in the bacilli, which continue to multiply freely in their sheltered situation in the gall-bladder. As convalescence begins, the obstructive swelling presently subsides, and the contents of the gall-bladder, passing freely into the intestine, convey with them a dosage of the typhoid bacilli and toxins sufficient to swamp and overcome the developing immunity, and a relapse ensues.

Such an explanation is conceivably the true one. There is no available evidence to the contrary, and it accords with results that can be obtained in the laboratory when animals which have acquired considerable immunity are submitted to a large overdose of the particular bacterium concerned.

## CHAPTER V

# IMMUNITY

By C. H. BROWNING

**Definition.**—Immunity may be defined as insusceptibility to infection with living organisms, or to the action of their products, so that when a given infective agent or its products gains access to the tissues of an immune individual disease does not occur. Of course, immunity also exists towards diseases of which the causal agents are as yet unknown—*e.g.*, scarlet fever. A characteristic feature of immunity is its specificity; thus, insusceptibility toward a given disease does not imply the existence of immunity toward any other disease. Further, the important fact must be borne in mind that immunity is in general only relative; an immune animal will be unaffected by a dose of the infective agent many times greater than that which is sufficient to cause disease in a susceptible animal, but a sufficiently large dose will lead to disturbances of health even in the insusceptible individual. Susceptibility depends frequently on the route by which the infective agent reaches the tissues. Such considerations regarding the effects of dosage and of the path of entrance of the infective agent make it clear why certain animal species are immune to a given disease under natural conditions, but can be readily infected experimentally—*e.g.*, the susceptibility of guinea-pigs to infection with *B. typhosus*. Immunity may be natural or it may be acquired. Acquired immunity is either active or passive. Active immunity is acquired as the result of an attack of the disease or of experimental inoculation; in the latter case the immunity is termed "artificial." Of very great importance both theoretically and practically is the fact that often the serum of an actively immune individual can confer immunity when injected into a susceptible animal, which is then said to be passively immunized. The conditions which lead to natural immunity are probably even more various and complicated than those which underlie acquired insusceptibility; accordingly, the phenomena of acquired immunity will be discussed in the first place.

**Artificially Acquired Immunity.**—*Active Immunity* is essentially the resistance to reinfection which accompanies recovery from an

attack of the disease. In producing such immunity for practical purposes, it is necessary to regulate the gravity of the infection so as to avoid the possibility of a fatal result. The production of a very severe illness should also be avoided, since it has been found that the highest degree of immunity does not result from an infection so severe as to endanger life. The severity of the effects of inoculation may be regulated in various ways: by injecting (1) attenuated organisms, (2) sublethal doses of virulent organisms, (3) dead organisms, or (4) the products of organisms (toxins) in sublethal doses. A high degree of immunity can ultimately be produced by commencing with the injection of small amounts, and increasing the doses slowly at suitable intervals. After ceasing to give further injections, a considerable degree of immunity is maintained for a long period. The particular procedure which will give the best result with a given organism must be ascertained by experiment. The name *antigen* is applied to any substance toward which immunity can be developed, as evidenced by the appearance of antibodies in the serum. *Passive Immunity* is produced by injecting into a susceptible animal the serum of one which has been rendered actively immune by the methods mentioned above, the serum of the actively immune animal being termed an *antiserum*. Passive immunity is at its maximum soon after the introduction of the antiserum, but tends to disappear much more rapidly than actively acquired immunity.

### Methods of developing Active Immunity.

#### *1. Cultures.*

The introduction of living organisms into the body of a susceptible animal affords the opportunity for multiplication to an extent sufficient to produce a fatal infection. To avoid the possibility of this consequence, it is necessary to adjust the virulence or the dosage of the infective material, so that spontaneous recovery, with the development of a certain degree of immunity, will result. This end may be attained by employing attenuated or dead organisms. In many instances, however, a high degree of immunity can be conferred only by the injection of highly virulent organisms. Such virulent bacteria may be employed to raise to a higher grade the immunity which has already been conferred by injections of dead or attenuated organisms. Virulent organisms may also be used from the commencement in the process of immunization, minute doses being employed at first; but this method has its limitations, since in the case of certain bacteria—*e.g.*, *B. anthracis* and organisms of the hæmorrhagic septicæmia group (fowl cholera)—the injection of a few bacilli, or even a single one, into a normal animal may cause a rapidly fatal infection.

(*a*) *Living Virulent Organisms.*—It is necessary to control the action of the living virulent pathogenic agent in some way so as to prevent the occurrence of an unmodified attack of the disease. A variety of procedures have been adopted to attain this object—*e.g.*: (1) Regulation of the dosage, so that the amount employed to begin with is below the lethal limit for a susceptible animal; (2) introduction of the virus by a route other than that through which natural infection occurs; (3) introduction along with the pathogenic agent of substances which modify its action. Ferran first employed a living culture of cholera spirilla in immunizing human subjects against cholera, the organisms being introduced subcutaneously. It is important to note that the pathogenic agent is introduced by a route other than that by which the natural infection takes place; the spirilla do not proliferate in the subcutaneous tissues, and are rapidly killed off. It is advisable, however, to commence immunization with attenuated cholera organisms to avoid severe local effects (necrosis). Koch immunized cattle against rinderpest by injecting subcutaneously the bile of animals dead of the disease. Certain constituents of the bile have a mitigating effect on the unknown virus which is present, since Kolle showed that if the infective bile is centrifugalized and the washed sediment is used for inoculation, the animals acquire the disease in an unmodified form. The action of virulent organisms may be modified by injecting at the same time the corresponding antiserum (see p. 152). This so-called *combined immunization* has proved to be a very valuable method in certain cases. In immunizing against protozoal diseases of cattle (piroplasmosis), a series of injections of increasing doses of blood of infected animals is given.

*Exaltation of Virulence.*—For purposes of immunization it is frequently necessary to employ cultures of organisms which are known to be highly virulent. Virulent cultures may be obtained—(*a*) By *passage* through a series of animals, usually of the same species, according to the method of Pasteur. A convenient method is to inoculate an animal intraperitoneally; when it dies, the peritoneal exudate is employed directly to inoculate another animal, or a culture is made which is then employed for the second inoculation. Intravenous injection may also be employed. Passage through an animal of a different species may cause exaltation of virulence; thus, Pasteur found that the bacillus of swine erysipelas was rendered more virulent for pigs by passage through pigeons. (*b*) By inoculation along with living or dead organisms of another species. In this way attenuated diphtheria bacilli are rendered virulent by injection along with streptococci; attenuated streptococci are increased in virulence by injection along with *B. coli*; dead cultures of *B. coli* increase the virulence of *B. typhosus*.

The resorption of living tumour cells and other tissues may under certain circumstances produce active immunity against subsequent

inoculation with virulent tumour. The destruction of protozoa in an infected animal's body through the agency of chemotherapeutic agents—*e.g.*, acetyl-para-amido-phenylarsenic acid, in the case of mice infected with *Trypanosoma Brucei*—leads to immunity.

(*b*) *Attenuated Organisms.*—Attenuation of virulence may be attained by—(*a*) Growth outside the animal body. In artificial culture media diminution in virulence usually becomes increasingly marked with the lapse of time. After repeated subculture the organisms may entirely lose their virulence; thus, pneumococci very rapidly become attenuated in culture. Various factors may be responsible for this attenuation—*e.g.*, air, light, and metabolic products of the organisms—in addition to the absence of certain conditions which exist in the animal body. Pasteur, in his original investigations on protective inoculation against fowl cholera, found that a bouillon culture of the fowl cholera bacillus had lost its virulence after several months when kept in the dark, but exposed to air; subcultures were also non-virulent. The culture so attenuated was then employed for inoculating fowls, which acquired a certain degree of immunity. On the other hand, a bouillon culture of the same organisms, if protected from air, may retain its virulence for six months (Kitt), and may still be virulent after subculturing over a period of years. Haffkine attenuated *V. cholerœ* by growing it in a current of air. Certain organisms tend to be comparatively stable as regards their virulence, which is retained with little alteration in artificial culture media under ordinary conditions. For such organisms special conditions can be devised which, while leaving the vegetative activity of the organisms practically unchanged, cause marked diminution of virulence. Thus, Pasteur attenuated the anthrax bacillus by prolonged growth at an abnormally high temperature (42° C.); Chamberland and Roux, in the case of the same organism, produced attenuation by the addition of a weak antiseptic (carbolic acid, 1 : 600) to the culture medium. Kolle succeeded in depriving plague bacilli of their virulence by growth in bouillon containing alcohol (0·5 to 5 per cent.) at 41° to 43° C.; after two to three months the organisms were attenuated to such an extent that inoculation with an agar culture did not infect guinea-pigs or monkeys, which were then protected against infection with a fully virulent strain. Other procedures have also been employed by which the organisms are subjected to conditions unfavourable to some extent to their growth—*e.g.*, Röntgen rays, compressed air, etc. (*b*) Passage through animals of another species. The classical example of this procedure is the permanent mitigation of smallpox virus for the human subject after several passages through cattle. A calf is inoculated with the contents of human smallpox pustules; material from the resulting lesion is employed to inoculate other calves. In this way, after several passages through cattle, a virus is obtained which, on inoculation into the human subject,

no longer produces the generalized symptoms and eruption characteristic of smallpox, but merely a local pustule at the site of inoculation, with comparatively slight disturbance of health. The modified virus never regains its original virulence. However often it is subsequently passed through the human subject, only a local lesion results; but the immunity thus conferred protects against an attack of generalized smallpox. Duguid and Burdon-Sanderson observed that anthrax bacilli were diminished in their virulence for cattle by passage through guinea-pigs, and Greenfield showed that the attenuation persisted in cultures made from the infected guinea-pigs. Pasteur found that the bacilli of swine erysipelas were diminished in their virulence as the result of passage through rabbits. Pasteur's method of immunizing sheep and cattle against anthrax depends on the employment of living attenuated organisms (see above). The animals receive two injections; the first, *premier vaccin*, consists of anthrax cultures which have been grown for twenty-four days at 42° C., and which are so attenuated that they can kill only white mice, but not guinea-pigs; the *deuxième vaccin* is given twelve days after the first injection, and consists of cultures grown for only twelve days at 42° C., which are sufficiently virulent to kill mice and guinea-pigs, but not rabbits. The immunization of cattle against tuberculosis has also been carried out on this principle. Behring's "bovovaccin" and Koch and Schütze's "tauruman" consist of living attenuated tubercle bacilli of the human type, which, when injected into calves intravenously, produce immunity against subsequent inoculation with virulent tubercle bacilli of the bovine type. A practical disadvantage of the procedure is the fact that the human bacilli used for immunization are not killed off; and, although no focal lesions are produced, living bacilli may be demonstrated after many months by the occurrence of tuberculosis in guinea-pigs which have been inoculated with apparently normal tissues from the immunized animals.

(*c*) *Dead Organisms.*—The injection of killed organisms in suitable, gradually increasing doses may in certain instances produce a high degree of immunity. Such is the case with *V. cholerœ* and *B. typhosus*, and subcutaneous injections of cultures of these organisms killed by heat have been employed to immunize human subjects. This is the method most commonly employed to produce antisera for laboratory purposes. Instead of heat, various disinfectants may be employed to kill the organisms—*e.g.*, chloroform, phenol-derivatives, etc. The immunizing effect of dead organisms is frequently much inferior to that produced by living bacteria, as in the case of the plague bacillus (Kolle and Otto). This may be due partly to chemical alterations produced in the process of killing, and partly to the fact that a certain degree of multiplication of organisms in the tissues is necessary to produce a powerful immunity reaction. Cultures killed by heat have been extensively applied by Wright

in the treatment of various chronic infections in the human subject.

(*d*) *Extracts of Organisms* (*Endotoxins*).—Instead of injecting the dead bacteria themselves, extracts may be prepared by macerating in various ways, and then separating the bacterial bodies by filtering through porcelain or by centrifugalizing. The resulting fluid (the "free receptors" of Neisser and Shiga) possesses immunizing properties. Again, the bacteria may be disintegrated mechanically (Macfadyen and Rowland), and the fluid product may be employed for immunizing. The intracellular substances with poisonous properties, or *endotoxins*, which are set free when the bacterial cells are disintegrated or dissolved, appear in some instances to be unable to exercise their effect when the intact bacilli are injected into the tissues, so that animals immunized against the latter are still susceptible to the endotoxins. Under certain circumstances the elaboration or liberation of such toxic bodies seems to occur most markedly in the body of an infected animal; thus, Roux and Chamberland found that the bacterium-free exudate of animals infected with the bacilli of malignant œdema was specially favourable material for use in developing immunity. Bail has investigated such toxic products formed within the animal body, which he has termed *aggressines*, and has concluded that they are not formed under any other circumstances. These aggressine-containing exudates have proved of great value in immunizing against organisms of the hæmorrhagic septicæmia group (swine plague, etc.). Wassermann and Citron have found that similar substances (artificial aggressines) can be extracted *in vitro* by treatment with water, or still better with fresh serum.

### *II. Separated Bacterial Metabolic Products or Toxins.*

Certain organisms in the virulent state bring about their harmful effects by means of poisonous products which they produce in the tissues, and which are termed *toxins*. In fluid cultures similar substances are formed, so that when the bacterial bodies are removed by filtration through porcelain—*e.g.*, a Chamberland candle—the bacterium-free fluid, when injected into a susceptible animal, produces almost all the phenomena of the naturally-occurring disease. Toxins which are "secreted" by the bacteria into the culture fluid are called *extracellular toxins*, or *exotoxins*. *B. diphtheriæ*, *B. tetani*, *B. botulinus*, all belong to the class of toxin-producing organisms. Similar toxic bodies are produced by certain plants and animals—*e.g.*, ricin and abrin, which are extracted by water from the seeds of *Ricinus communis* and *Abrus precatorius* respectively, and the poisons of snakes and scorpions. The process of immunization against toxins is begun by the injection of minute doses which will produce no severe pathogenic effects; subsequent

injections are administered at suitable intervals, and the dose is progressively increased till many times the original fatal dose may be given at one time. This is the procedure employed in obtaining diphtheria and tetanus antitoxins from horses. The method does not succeed in certain cases; thus, on attempting to immunize small animals with tetanus toxin, it was found that successive injections of minute fractions of the fatal dose produced supersensitiveness instead of immunity (see p. 177). In such cases immunity can be produced by injecting, to begin with, altered toxin which has been deprived of its poisonous action by heating (Ehrlich) or by treatment with chemicals—*e.g.*, iodine trichloride (Behring); and then, after a certain degree of resistance has been developed, untreated toxin can be employed to raise the immunity still farther.

*The mode of application of the immunizing agent* is of considerable importance when the production of immunity is aimed at. It is necessary to consider the dosage of the immunizing material, the intervals between the administrations, and the site of inoculation. For the development of a high grade of immunity those factors must be regulated according to the species and the individual characters of the animal, and to the immunizing agent employed. The individual factor in the animal employed is important; thus, certain horses are incapable of producing potent diphtheria antitoxin. The following facts are of general application: The *dosage* of toxin must be such that severe illness does not follow; at the same time a certain degree of reaction must be produced. It is usually best to begin with small doses, which are subsequently increased. The *interval* between doses must be arranged so as to avoid the administration of antigen when there is a state of supersensitiveness (see p. 177). The *sites of inoculation* which may be selected are subcutaneous, intravenous, and intraperitoneal. The differences in these situations depend on chemical as well as anatomical conditions, and influence the result of inoculation. The comparatively non-cellular subcutaneous tissue delays absorption and modifies the injected material; thus, the fatal dose of diphtheria toxin for guinea-pigs is more than twice as great when it is injected subcutaneously than when administered by the intravenous route. The antitoxin production is also greater after subcutaneous injection in the case of diphtheria toxin. After subcutaneous injection of toxins local lesions tend to occur (necrosis, etc.); after intravenous injection generalized reactions and toxic phenomena are more pronounced features. Accordingly, it is comprehensible that in certain cases a dose of antigen which has a powerful immunizing action when injected intravenously may be quite ineffective subcutaneously, as Tallquist found in the case of the lysin produced by V. Nasik. It is an important fact that the protective action of immunization may depend on the route by which the infective agent reaches the tissues; thus, guinea-pigs treated by sub-

cutaneous or intraperitoneal injections of *V. cholerœ* are protected against intraperitoneal infection, but not against infection by feeding. Immunity may be produced by feeding, but in most cases it is not of high grade. The most striking example of this method is the original observation of Ehrlich, that mice fed with ricin and abrin after some weeks tolerated the subcutaneous injection of 400 times the original fatal dose. As a rule, however, the immunizing substances are too far decomposed in the alimentary canal to produce immunity, and the antigens must be introduced directly into the tissues—*i.e.*, parenterally.

### *Practical Application of Active Immunization.*

It has long been known that a mild attack of a disease frequently protects against a later infection not less efficiently than a severe primary attack does. Hence the object of *prophylactic inoculation* is to confer immunity against subsequent infection by producing an attack of the disease of mitigated severity. The method is of practical value in the case of smallpox (Jennerian vaccination), inoculation of sheep and cattle against anthrax (Pasteur), antityphoid inoculation (Wright and Semple, Leishman), hydrophobia (Pasteur), anticholera and antiplague inoculation (Haffkine). Within recent times the method of active immunization has been widely employed for *curative* purposes. In the case of chronic localized infections—*e.g.*, furunculosis due to staphylococci—Wright and Douglas found that the patient's blood-serum was deficient in substances which enabled the leucocytes to ingest the cocci. They viewed this deficiency of the serum as an indication of lowered resistance which predisposed to infection. Owing to the localized character of the lesions, and the surrounding granulations and indurated connective tissue which hindered absorption, the organisms present were unable to exercise an immunizing effect. Accordingly, the immunity is raised by subcutaneous injections of the corresponding organisms killed by heat, such suspensions being called *vaccines*, the dosage being reckoned according to the number of bacteria injected. Thus, it is supposed that by raising the content of the serum in immune substances, as measured by the opsonic index (see p. 158), and by adopting procedures which increase the flow of lymph to the site of the lesion, the leucocytes are enabled to dispose of the infecting organisms. Satisfactory results have been obtained by vaccine treatment in furunculosis, acne, and tubercular and pyogenic genito-urinary affections, etc. Vaccines have also been employed in the treatment of acute generalized infections, but the rationale is not clear.

### Properties of the Serum and Cells of Highly Immunized Animals.

The serum of a highly immune animal, A, when injected into another animal, B, of normal susceptibility, protects the latter against inoculation with a certain amount of the same pathogenic agent as had been employed to immunize animal A. The animal B is then said to be passively immunized. The antiserum may be introduced intravenously, intramuscularly, intraperitoneally, or subcutaneously. In certain cases anti-substances may be absorbed from the alimentary canal—*e.g.*, when a young animal drinks the milk of an immunized female of the same species. Passive immunity is of shorter duration than active immunity; the antiserum exerts its maximum effect when injected simultaneously with the pathogenic agent, but within certain limits it can exert both prophylactic and curative action. Immunity inherited by the young of an actively immunized mother appears to be merely passively transferred. The action of an immune serum is *antitoxic* if it is derived from an animal which has been immunized against the toxic products of bacteria, and consequently neutralizes their toxins; or *antimicrobic* if developed by injecting the bacteria themselves, and hence possesses the property of preventing infection with the organisms. Antisera, in addition to their effect *in vivo* may produce obvious alterations on the corresponding antigens *in vitro*. The properties of antisera have been very thoroughly investigated, with a view to elucidating the nature of immunity. An enormous number of facts has been accumulated, which have served as a basis for several theories; but no explanation which is applicable to all the phenomena has yet been advanced.

**The Character of Antigens—Specificity.**—Substances which have the property of giving rise to antibodies when introduced into an animal's tissues are termed "antigens." Chemically they are undefined, as they have never yet been isolated in a pure state; they cannot be dissociated from proteins, and are most likely highly complicated protein derivatives. The essential antigenic constituents are fairly stable, and are probably very minute in amount. Thus, Jacoby separated ricin toxin from the greater part of the accompanying protein by digestion with trypsin. But the prolonged action of digestive ferments destroys antigens in general. There is no conclusive evidence in favour of the view recently advanced, that antigens are of lipoid nature. The following bodies belong to the class of antigens—bacterial and animal toxins, phytotoxins (ricin, abrin, crotin), animal tissues (red blood-corpuscles, spermatozoa, etc.), ferments (rennin, trypsin). On the other hand, there is no poison of known constitution—*e.g.*, alkaloids or glucosides—to which an antiserum has been obtained. An intermediate position is, however,

occupied by bodies like carbohydrates ; when these are introduced directly into the tissues, the blood-serum acquires the property of splitting them, in virtue of having developed ferments which are not normally present (Abderhalden). The antibodies which are developed in response to a given antigen are specific ; that is to say, an animal which has been immunized against a certain substance, X, develops in its serum antibodies with a specific affinity only for the antigens contained in X ; towards all other antigens the serum behaves like that of a normal animal of the same species. Ehrlich's conception of specificity is that it depends solely on chemical constitution. This view affords a rational explanation of the fact that an antiserum to one organism may have a certain degree of action on an allied bacterium, since the two organisms must contain certain antigens in common. Antibodies appear in the serum usually five to ten days after the injection of the antigen. The same antigen, if injected into two different species, does not produce identical antibodies, although the so-called combining groups appear to be similar; this is well illustrated by the great differences in the behaviour of different immune bodies, obtained by injecting blood of one species into various animals, along with different complements (see p. 154).

### *Antitoxic Sera.*

As has been seen, filtrates of bouillon cultures of *B. diphtheriæ*, etc., when injected into susceptible animals, produce the symptoms of the naturally-occurring disease. As the result of appropriately graduated and spaced injections of toxic filtrates into suitable animals, an antiserum can be obtained which neutralizes the toxin. This was first demonstrated in the case of tetanus and diphtheria toxins by Behring along with Kitasato and Wernicke. A fatal dose of toxin mixed with sufficient antiserum, and then injected into a susceptible animal—*e.g.*, a guinea-pig—is without any harmful effect ; normal serum lacks this neutralizing action. The following are the general facts with regard to the formation of antitoxin and its action with toxin. *Origin of Antitoxin.*—Antitoxin is elaborated by the tissues of the actively immune animal. This is proved by the fact that, when horses immunized with tetanus or diphtheria toxin have been repeatedly bled until almost all their blood has been removed, the regenerated serum still contains the same amount of antitoxin as before bleeding ; also pilocarpine causes an increase in the antitoxin content of the blood. The view once held, that antitoxin is merely altered toxin, is further disproved by the observation that a horse may develop an amount of tetanus antitoxin capable of neutralizing 100,000 times the quantity of toxin injected. *Mode of Action of Antitoxin.*—(1) Antitoxin combines directly with toxin without the mediation of the tissues. Thus, ricin agglutinates red blood-corpuscles *in vitro ;* if antiricin serum is mixed with the ricin,

and blood is then added, no agglutination occurs. This demonstrates antitoxic action in the test-tube. (2) The combination of toxin with antitoxin proceeds like a chemical reaction : (*a*) Neutralization proceeds more rapidly at higher temperatures (37° C.) than at lower (20° C.), and more rapidly in concentrated than in dilute solutions ; (*b*) the law of multiples holds strictly ; thus, if one volume of antitoxin neutralizes ten lethal doses of toxin, then ten volumes of antitoxin will be required to neutralize a hundred lethal doses of toxin. The neutralizing reaction occurs comparatively slowly, but varies according to the particular toxin. Martin and Cherry demonstrated this by filtering mixtures of equivalent quantities of snake venom and antivenin through porcelain filters impregnated with gelatine. The toxin by itself passes through such a filter, but antitoxin does not. If the mixture is filtered shortly after mixing, free toxin is obtained in the filtrate ; but if the mixture is first allowed to stand for some time (half an hour), then the filtrate is non-toxic. Again, these workers found that a neutral mixture, when heated at 80° C. shortly after mixing, becomes toxic owing to destruction of the antitoxin ; but if the mixture is allowed to stand for more than a quarter of an hour before heating, then the toxicity is not restored. In animal experiments, the difference in the toxicity of old and of recently-made mixtures is more marked when they are injected intravenously than when subcutaneously. This led to the hypothesis that the subcutaneous tissues contain catalytic agents which accelerate the combination (Morgenroth). The combination of toxin and antitoxin is at first reversible, but becomes firmer with the lapse of time. Before firm combination has taken place dissociation may be produced by dilution of the toxin-antitoxin mixture ; thus, *in vitro* a small quantity of a partially neutralized recent mixture of arachnolysin with its antiserum, when diluted, is more actively hæmolytic than a large amount undiluted. The same holds good in the case of *B. botulinus* toxin and its antitoxin when injected intravenously in rabbits (Otto and Sachs). (3) The effect of the antitoxin is not to destroy the toxin, but to form a non-toxic combination with it. This has been conclusively demonstrated in a number of cases by the observation that hydrochloric acid causes dissociation of the toxin-antitoxin combination (Morgenroth). In this way neutral mixtures which have stood for a long time can be rendered toxic again, as has been shown for diphtheria toxin, botulinus toxin, abrin, etc. The *chemical nature of antitoxins* has not been determined. They are associated with the serum globulins. An immune serum shows no characteristic change beyond the specific property of antagonizing the corresponding antigen.

**The Standardizing of Antitoxic Sera.**—The great therapeutic efficacy of diphtheria antitoxin rendered the exact determination of the potency of antitoxic serum extremely important. Toxins are very unstable ; hence the preservation of a standard toxin is im-

practicable. On the other hand, antitoxic serum, when dried and preserved in air-free glass bulbs at room temperature away from light, maintains its potency unaltered for an indefinitely long time. Ehrlich accordingly devised the following method: The toxicity of a given specimen of diphtheria toxin was determined accurately, the amount necessary to kill a guinea-pig of 250 to 280 grammes weight in precisely four days, when injected subcutaneously, being taken as the minimum lethal dose (M.L.D.). This estimation is very accurate, as guinea-pigs show a remarkably constant susceptibility to diphtheria toxin. Then the smallest amount of antitoxic serum was ascertained which, when mixed with 100 M.L.D. of the same toxin and injected subcutaneously into a similar guinea-pig, did not cause the slightest reaction. This amount was termed the "immunity unit" (1 I.E.—Immunization-Einheit). The amount of toxin precisely neutralized by 1 I.E. of antitoxin is termed the "Lo dose"; the amount of toxin which, when mixed with 1 I.E. of antitoxin, leaves 1 M.L.D. of toxin free, so that a guinea-pig injected with the mixture dies on the fifth or sixth day, is called the "L + dose." The L + dose can be more accurately determined than the Lo dose; hence the former is employed in standardizing the antitoxin. If 1 c.c. of the antitoxic serum is required to neutralize the toxin, then this amount is equivalent to one unit of antitoxin; if 0·01 c.c. is required, then 1 c.c. of the serum is equivalent to 100 units. A powerful serum may contain over 1,000 units per cubic centimetre. The potency of the standard serum being thus determined, it is possible to titrate an unknown serum at a period when the original toxin is no longer available. This is done in the following way: The L + dose of the new specimen of toxin along with 1 I.E. of the standard antitoxin is accurately determined. Then the quantity of the unknown antitoxic serum which is exactly sufficient to leave 1 M.L.D. free when mixed with this amount of toxin must contain 1 I.E. Such a procedure is necessary on account of the fact that a given number of fatal doses of two different specimens of toxin may not be neutralized by precisely the same amount of a given antitoxic serum; the theoretical importance of this phenomenon is referred to later. To be of practical value, the potency of an antitoxic serum as ascertained by this method must correspond with its therapeutic efficiency when infection has occurred prior to the administration of the serum. The balance of evidence supports this view (Banzhaf, Berghaus), although Roux and Kraus hold that there is no necessary connection between the two functions. Roux estimates the antitoxic content of a serum by its therapeutic effect when injected into a guinea-pig twelve hours after inoculation with a given amount of virulent diphtheria culture.

**Practical Application of Antitoxin Treatment.**—The use of antitoxin in the treatment of diphtheria has effected a very great saving

of life. To secure the best results, it is important to employ a sufficient dose and to administer the antitoxin as early as possible, since experiments have shown that, when once toxin has combined firmly with the cells, its dissociation can be effected only by enormous doses of antitoxin, if at all; at first, however, the combination is less firm. The most rapid action of antitoxic serum is secured by intravenous injection (Henderson Smith); intramuscular injections are fairly rapidly absorbed; but absorption from the subcutaneous tissue into the circulation occurs comparatively slowly. Antitoxin has proved of comparatively little value as a curative agent in tetanus, since the symptoms occur when the toxin has already entered into firm combination with the cells of the nervous system. In veterinary operations, however, tetanus antitoxin is useful as a prophylactic agent.

### *Theories regarding the Constitution of Toxins, the Nature of the Toxin-Antitoxin Reaction, and the Formation of Antibodies.*

The general phenomena of antitoxic action have already been described. In order, however, to obtain an insight into the mechanism by which the body elaborates protective substances, it is necessary to arrive at a conception of the structure of toxins and the way they exert their harmful effects. Intimately bound up with these problems, also, is the question as to the exact nature of the processes involved in the neutralization of toxin by antitoxin.

The action of a toxin occurs in two phases. Thus, when tetanus toxin is injected into a rabbit, there is for a considerable period no disturbance; but the toxin disappears very rapidly from the circulation, and after a short time the injection of large amounts of antitoxin does not prevent the appearance later on of the characteristic symptoms. Accordingly, the first phase consists in the combination of the toxin with the tissues, and the second in the toxic action which leads to disturbance of function. Frogs when injected with tetanus toxin and kept at 8° C. do not show any symptoms; but the toxin combines with the nervous system, and a subsequent injection of antitoxin does not prevent the occurrence of tetanus when the temperature is raised to 32° C. (Morgenroth). Therefore Ehrlich has supposed that the toxin molecule contains two sets of atom groups—(*a*) the *haptophore*, which enables the toxin to enter into combination with the tissue cells, this being an essential condition before (*b*) the *toxophore* group can act. It is not necessary that every cell with which the haptophore group combines should be susceptible to the action of the toxophore group. Thus, rabbits are much less susceptible than guinea-pigs to the subcutaneous injection of tetanus toxin; but both animals are equally susceptible to intracerebral administration. The explanation is that the rabbit's liver and spleen bind some of the toxin introduced sub-

cutaneously, whereas the only organ of the guinea-pig which has an affinity for the toxin is the nervous system, on which the whole effect of the toxin is concentrated by whatever route it is introduced.

The occurrence of a latent period between the injection and the occurrence of symptoms is characteristic of toxins; the duration of the latent period depends to some extent on the amount of toxin injected, being shorter the larger the dose up to a certain limit. Certain toxins, however—*e.g.*, that of V. Nasik—act without an incubation period. Ehrlich conceives that the development of antitoxins occurs in the following fashion: A molecule of cellular protoplasm, on the analogy of benzol compounds, consists of a central nucleus which elaborates side-chains for the performance of its functions. The haptophore group of a toxin molecule combines with a particular side-chain or *receptor* of the protoplasm molecule, and renders it useless for further functional purposes. Therefore, in order that this function may be maintained, such receptors require to be regenerated, and, in accordance with Weigert's observations on hypertrophy, over-regeneration occurs, the excess of new-formed receptors no longer remaining sessile—*i.e.*, attached to the nucleus—but being cast off free into the plasma, where they act as molecules of antitoxin. Hence the same receptors which when sessile lead to the anchoring of toxin and supply the condition necessary for intoxication, when set free into the plasma act as protective agents. Conversely, also, the haptophore group of the toxin, which, by combining with the cellular protoplasm, stimulates the production of antitoxin, is identical with that portion of the toxin molecule which the antitoxin combines with. This identity is an essential point of ***Ehrlich's side-chain theory***, as the hypothesis outlined above is termed. On the analogy of the stereochemical relationships which, according to E. Fischer, exist between a ferment and the substrate on which it acts, the antitoxin has been said to fit the toxin as a lock fits a key. Clearly, then, the necessary condition for antitoxin production is that the toxin should enter into combination with the cellular protoplasm; accordingly, antitoxin may be formed by tissues which anchor the toxin, but are not susceptible to the toxophore group. Thus, although the alligator and the hen are highly resistant to tetanus toxin, their tissues possess some degree of affinity for the toxin, and they develop antitoxin; on the other hand, the turtle's tissues do not combine with the toxin at all, and this animal produces no antitoxin. It is evident that for the development of antitoxin the existence of the toxophore group should be of subsidiary importance. Experiments confirm this, since *toxoids—i.e.*, toxins which have been deprived of their toxic action in various ways—lead to antitoxin formation. It must be admitted that no actual proof exists as to the identity of the antitoxin molecules with the cell receptors which fix the toxin. The fact that the grey

cerebral matter is the only tissue of the guinea-pig which fixes tetanus toxin was held to prove this identity (Wassermann and Takaki, Dönitz); but lipoid constituents of brain matter, which are certainly not antitoxin, also have this effect.

Highly divergent views have been held as to whether the toxic products of bacteria are homogeneous or not, and as to the nature of the process whereby antitoxin neutralizes them. Ehrlich concluded that—(*a*) most crude toxins are not homogeneous, but consist of a variety of different molecules; and (*b*) the combination of toxin with antitoxin is firm, and resembles that between a strong acid and a strong base. The complex character of toxins appeared from the following experiments with diphtheria toxin: (1) *The Ehrlich Phenomenon.*—If an estimation is made of the number of lethal doses of crude toxin which can be exactly neutralized by the immunity unit of antitoxin, then it is found that this amount must be increased by considerably more than a lethal dose, in order that the mixture may contain one free lethal dose of toxin. Ehrlich's explanation is that the crude toxin contains, in addition to the true toxin molecules, others of epitoxoid which have a degenerated toxophore group, and whose haptophore group is of weaker combining power than that of the true toxin molecule. In the neutral mixture a certain number of antitoxin molecules are combined with epitoxoid; when more crude toxin is present, however, these antitoxin molecules will combine instead with molecules of true toxin, so that an excess of more than one lethal dose of toxin must be added in order that one dose may remain free. (2) The method of *adding to a given quantity of toxin varying fractions of the neutralizing dose of antitoxin* is a procedure which has also been employed by Ehrlich in order to determine the constitution of crude toxin. He found, on estimating the toxicity of a series of mixtures of toxin with increasing fractions of the neutralizing dose of antitoxin, that the diminution in toxicity cannot be represented by a continuous curve, but occurs in a "step and stair" fashion, thus indicating that the crude toxin consists of a mixture of molecules differing both in their combining and in their toxic properties. In this way Ehrlich distinguished *proto-*, *syn-*, and *epitoxoid*, with combining affinities respectively greater than, equal to, and less than, that of toxin, and also *toxone*, with little affinity for antitoxin, which is usually present in very minute amount in crude toxin. When a guinea-pig is injected with a large dose of toxin neutralized with antitoxin, the action of the accumulated toxone manifests itself by paralysis and wasting, which occur after some weeks. A further indication of the conversion of toxin into toxoid with degenerated toxophore but intact haptophore group is the fact that a crude toxin which has lost much of its toxicity as the result of keeping may still require the same amount of antitoxin to neutralize it as was originally necessary. (3) The *Danysz-Dungern Phenomenon* consists in the

fact that the amount of toxin which is neutralized by a given quantity of antitoxin is greater when the toxin is added all at once than when it is added in fractions. In terms of Ehrlich's hypothesis, this phenomenon is due to the presence of epitoxoids.

*Arrhenius and Madsen's theory* is that toxin and antitoxin combine, like bodies with weak chemical affinity, according to the Guldberg-Waage law of mass action; so that any given mixture contains free toxin and free antitoxin molecules in addition to the dissociable complex toxin-antitoxin, the proportions depending on the relative amounts present of toxin and antitoxin. It is difficult to reconcile this view with the Danysz-Dungern phenomenon. On the other hand, *Bordet's theory*, that the union is a process of colloid adsorption, and that a given amount of toxin can combine with varying quantities of antitoxin, affords a rational explanation of the Danysz-Dungern experiment; but it takes too little account of the undoubted quantitative relationships which do exist. It has not been shown that either toxin or antitoxin is a colloid; but these bodies are associated with colloids, hence it is not surprising that their reactions should exhibit colloid characters. Whether the neutralization of toxin by antitoxin depends ultimately on alterations of surface tension (Zangger) or on chemical changes in amphoteric colloids (Landsteiner) is as yet undetermined.

### *Antibacterial Sera—Antisera to Tissue Constituents.*

The serum of an animal which has been rendered highly immune towards a given bacterium possesses the property of protecting a susceptible animal against infection with the organism in question. The antiserum may produce a variety of effects on the corresponding bacteria: (1) It may cause solution (*bacteriolysis*) or kill them (*bactericidal action*); (2) it may render them susceptible to ingestion by leucocytes (*opsonic, bacteriotropic action*); and (3) it may produce clumping of the organisms in a suspension (*agglutination*), or flocculation of bacterial constituents (*precipitation*). Knowledge of these processes has been greatly increased as the result of studying the action of antisera obtained by injecting tissue constituents—*e.g.*, red blood-corpuscles, serum, etc. The protective action of antimicrobic sera differs from that of antitoxic sera in not obeying the law of multiples (see p. 147); thus, if the amount of serum is determined which protects an animal against the lethal dose of bacteria, 100 times this amount of serum will not necessarily protect against 100 lethal doses. In fact, a limit is reached in the amount of infective material beyond which no amount of antiserum, however great, will confer protection. Again, the antiserum has no effect unless the amount present exceeds a certain limit. Neufeld and Händel found that 0·2 c.c. of antipneumococcus serum protected a mouse against 100,000 lethal doses, but 0·002 c.c. of the serum did not protect against the minimum lethal dose.

*Lysogenesis (Bacteriolysis, Hæmolysis)—Bactericidal Action.*

Nuttall originally observed that normal serum had a bactericidal effect on various organisms *in vitro*, and Behring and Nissen found that a guinea-pig immunized against *V. Metchnikovi* possessed the property of killing that organism. Pfeiffer injected cholera vibrios and anticholera serum into the peritoneum of a normal guinea-pig, and thereafter at intervals examined by the microscope samples of the peritoneal contents withdrawn by means of capillary tubes. He found that when sufficient immune serum was present the vibrios rapidly became transformed into poorly-staining granules (after ten to twenty minutes). This process, known as the *Pfeiffer phenomenon*, occurs without any co-operation of cellular elements in the peritoneum. The same result occurs on injecting the organisms alone into the peritoneum of an actively immune animal. The conditions in the tissues are not everywhere so favourable for bactericidal action as in the peritoneum; thus, bacteria in the capillaries are protected from free access of the plasma, just as in Buchner's experiment *in vitro* a bactericidal serum fails to kill the organisms when they are enmeshed in cotton-wool which has been moistened with the culture. Bacteriolysis occurs *in vitro* only with fresh immune serum, not with serum which has been heated for an hour at 55° C. But heated serum is equally as effective as fresh serum in the animal experiment. The action is restored in the test-tube by the addition of fresh normal serum to the heated serum, which by itself is without effect. Typhoid bacilli are similarly lysed; other organisms —*e.g.*, *B. pestis*—may be killed without the rapid occurrence of granule formation. In other cases, again—*e.g.*, staphylococci—bactericidal action does not take place, although immune substances are present in the antiserum. The mechanism of lysogenesis has been investigated very thoroughly in the case of hæmolytic sera by test-tube experiments (Bordet, Ehrlich, Muir), and the results have been found in general to apply to antibacterial sera.

**Hæmolysis.**—The fundamental experiments are as follows: (1) If red blood-corpuscles of an animal of species A are injected repeatedly into an animal of species B, the serum of the latter acquires the property of hæmolyzing the corpuscles of A. Thus, ox's red blood-corpuscles freed from serum, and suspended in isotonic (0·85 per cent.) NaCl solution, undergo hæmolysis at 37° C. on the addition of fresh serum of a rabbit which has been injected intraperitoneally with ox's red blood-corpuscles—immune serum; *i.e.*, the blood becomes laked owing to some alteration in the stromata which permits the hæmoglobin to diffuse out; the stromata persist as shadows. (2) The immune serum, after heating for one hour at 55° C., causes no laking of the blood-suspension; *i.e.*, the hæmolytic power of the serum has been destroyed. (3) Fresh rabbit's serum, which by itself has no effect, along with the heated immune serum causes

hæmolysis of the blood-suspension. Instead of normal serum from a rabbit, that of another animal—*e.g.*, the guinea-pig—may be used. These experiments show that in the production of lysis two bodies are concerned—the one developed as the result of immunization, which is relatively thermostable (immune body, amboceptor, substance sensibilisatrice); the other present in normal serum, which is thermolabile (complement, alexin, addiment, cytase).

**Conditions of Action of Immune Body and Complement.**—Immune body and complement react with the red corpuscles under quantitative conditions; thus, the amount of each component which will lyse a given amount of blood can be accurately determined. The quantity of immune body which is required to effect complete lysis of a given amount of blood-corpuscles depends to some extent on the quantity of complement present; thus the lytic dose of immune body is a minimum when the complement is in excess. Similarly the lytic dose of complement is a minimum when the immune body is present in excess. Immune body is increased in the serum as the result of immunization. It resists heating at 55° C.; it is specific within the limits already described. The immune body has a great affinity for the homologous antigen, and much more can be taken up by the red corpuscles than is required to produce lysis. A serum can be deprived of its immune body by treating with the corresponding red corpuscles at 0° C. (Ehrlich and Morgenroth). Blood-corpuscles so treated, when freed from serum, do not manifest any alteration in their resistance to physical agencies; they are, however, *sensitized*, so that they undergo lysis on the addition of complement. Immune body can be dissociated from sensitized corpuscles; simple contact with unsensitized blood causes a portion of immune body to pass over to the latter (Morgenroth, Muir); this dissociation occurs even when the sensitized corpuscles have been saturated with complement (Muir). Muir and Browning observed that, on filtering a mixture of immune body and complement through a Berkefeld filter at 37° C., the former passes through quantitatively, while the latter is retained, which indicates that the immune body and complement are not united. These experiments are not in favour of Ehrlich's view that the immune body is an amboceptor—*i.e.*, an intermediate link between the receptor of the red corpuscle and the complement. The species of animal from which the immune body is derived is of prime importance in determining whether or not a given complement can act so as to cause lysis; thus, Muir has shown that the immune body from the cat and from the rabbit both combine with the same receptors of ox's blood-corpuscles, and both lead to the absorption of horse complement; but hæmolysis occurs only when the complement is taken up through the agency of the cat's immune body. During the process of immunization the immune body undergoes qualitative changes (Browning and Wilson). *In vivo* hæmolytic immune body produces much the same effects as *in vitro*, but certain

quantitative differences exist; thus, Muir and M'Nee found that, when rabbits were injected intravenously with an immune body for rabbit's blood obtained from a goat, much more blood was lysed than could be accounted for by the hæmolytic power of the immune serum as estimated *in vitro*. The process of hæmolysis in the body also extended over several days. Complement is a normal constituent of serum, and does not undergo increase in an immunized animal. It is very labile, and is readily damaged by physical agencies, such as light, shaking, etc.; heating for one hour at 55° C. destroys it. The optimum temperature for its action is 37° C., and it ceases to combine at 0° C. Complement has very little affinity for the red corpuscles by themelves; bacteria, on the other hand, may absorb a considerable amount, but in either case the combination of antigen with antibody has a greatly enhanced affinity for complement. Complement combines very firmly, and in general it cannot be recovered again by dissociation. Bordet regards the immune body as producing a physical change in the red corpuscle, which increases its power of absorbing complement. This view, however, neglects the quantitative nature of the reactions; thus, Muir found in certain cases that the addition to the red corpuscles of multiple doses of immune body caused a corresponding increase in the amount of complement absorbed, so that much more than the hæmolytic dose might be taken up. The action of complement on sensitized corpuscles resembles that of a toxin. Combining action and toxic effect must be distinguished. Complement may fail to act (1) because it does not combine, or (2) owing to lack of toxic power. Serum which has been heated at 55° C. contains *complementoid*—*i.e.*, complement molecules whose zymotoxic group has been destroyed, but whose combining group is more or less intact. Thus, red corpuscles sensitized with multiple doses of immune body, and lysed by the minimum dose of complement, can combine with complementoid, which then serves to prevent the fixation of further amounts of complement. The question as to whether serum contains a single complement or a multiplicity has not been definitely settled. Ehrlich and his collaborators have brought forward much evidence in favour of the view that normal serum contains a variety of complements to suit different immune bodies, while Bordet maintains the unity of complement. The difference in opinion is due in part to differences in the methods of investigation employed. Thus, red corpuscles saturated with immune body will deprive a serum of all its complementing action. On the other hand, a serum from which the complement has been partially removed by a weak absorbing agent may in its action differ qualitatively from the untreated serum. Differences undoubtedly do exist in the complement molecules of a serum. Muir and Browning found that the addition of a very small amount of dead organisms to a normal serum deprives it of its bactericidal action

for organisms of another species, but leaves the amount of complement as tested by hæmolysis unaltered. The conclusion is therefore justified that there are molecules of bacteriophilic complement specially concerned in bactericidal action. The action of fresh serum in causing hæmolysis along with cobra venom, while not due to lecithin, is certainly distinct from the property of complementing immune body. Complementing effect is apparently due to the co-operation of several factors (Ferrata). When fresh guinea-pig's serum is diluted with distilled water, and carbonic acid gas is passed through the mixture, a portion of the globulin is precipitated; if the globulin precipitate is separated and redissolved, it is found that neither this constituent nor the albumin fraction by itself in amounts equivalent to many times that present in the hæmolytic dose of the native serum may have any lytic effect on sensitized corpuscles; but if the two fractions are mixed in corresponding proportions, the original activity is restored. Sensitized red corpuscles fix the separated globulin fraction, but not the albumin; these fractions have therefore been termed "middle" and "end" piece respectively (Brand); but the distinction between these components is not so sharply defined as that between immune body and complement. Recent work on the relationships of the complement components of different sera points to the end piece as being the more variable factor. Red corpuscles, along with large amounts of immune body, can remove the middle piece from complement-containing serum at 0° C. (Sachs and Bolkowska). Sensitized corpuscles united with complement middle piece are said to be *per-sensitized*. Complement can be split up by other procedures—*e.g.*, dialysis, the addition of weak HCl, etc. *The Nature of Complement* is quite obscure; so far it is known only as a property of fresh serum, and there is no sound basis for the identification of complement with lipoids (Liebermann), although lipoids may markedly influence complementing action (Cruickshank and Mackie). *The Origin of Complement.*—Metchnikoff denies that complement normally exists in a free state in the blood-plasma, and holds that it is liberated from the leucocytes when they are damaged. The balance of evidence is against this view. Thus, on injecting into an animal's circulation some of its own corpuscles sensitized with homologous immune body, hæmolysis occurs, whereas untreated corpuscles remain intact. Complement is rapidly regenerated, but little is known as to its origin. It cannot be demonstrated in any of the tissues, most of which have the power *in vitro* of fixing complement.

**Cytotoxic Sera.**—Immune bodies can be obtained for a variety of tissue cells—*e.g.*, spermatozoa, leucocytes, etc. A general law is that animals do not produce antibodies to their own tissues (autolysins), and only with difficulty to the cells of other members of their own species (isolysins). The autohæmolysin found in the serum

of cases of paroxysmal hæmoglobinuria is exceptional; but there is practically always an accompanying syphilitic infection, which may alter the reacting power of the tissues. A cytotoxic serum usually acts on the cells of other organs than that used for immunization, but it is, of course, specific for the species. Toxic effects are produced by the injection of such sera. Where the immune serum along with complement *in vitro* produces no obvious alteration in the cells, the occurrence of a reaction may be demonstrated by the fact that the complement has been absorbed. This is shown by adding to the mixture at a later stage sensitized red corpuscles, which remain intact owing to the absence of free complement.

Bactericidal action *in vitro* differs from hæmolysis in one striking respect—namely, that if an excess of immune body is present the organisms are not killed off. This constitutes the *phenomenon of Neisser and Wechsberg;* no satisfactory explanation has been offered, but analogous effects are observed in reactions between colloids.

**Bactericidal and Lytic Action of Normal Sera.**—Normal serum can kill a variety of organisms; to this property Buchner originally applied the term *alexin action*. In the same way certain normal sera cause hæmolysis of the blood of other species—*e.g.*, the serum of many guinea-pigs lyses ox blood. Normal lytic action has been shown in certain cases to be due to the co-operation of complement with a normal immune body. Thus, ox's red corpuscles at 0° C. remove the normal immune body from guinea-pig's serum, leaving the complement in the fluid; the corpuscles are then sensitized, and lyse on the addition of complement. But it has not been proved that alexin action is always due to two bodies. Normal antibodies are usually less stable than immune substances, and have less marked affinity for the antigen.

### *Opsonins, Bacteriotropins.*

The action of serum in rendering organisms susceptible to phagocytosis was first of all demonstrated by Denys and Leclef in 1895. They showed that an antistreptococcal immune serum induced phagocytosis by acting on the corresponding organisms, and not on the leucocytes. The researches of Wright and Douglas drew special attention to the importance of the subject. In their first communication they showed that—(1) The phagocytosis of staphylococci by human leucocytes depended on bodies present in normal human serum, to which they gave the name of *opsonins;* (2) leucocytes freed from serum by washing with salt solution did not ingest the cocci; (3) heating at 60° C. deprived the serum of its action; (4) the serum acted on the cocci; thus, if the cocci were treated with serum, and were then thoroughly washed, they were ingested when placed in contact with washed leucocytes; (5) no action of the serum on

the washed leucocytes could be demonstrated. The phagocytosis of inorganic particles may be aided by fresh serum; the cause of this phenomenon is quite obscure. In order to compare the opsonic power of the sera of different individuals, Wright and Douglas introduced a method which is a modification of that devised by Leishman: Standard emulsions of organisms and of washed leucocytes are prepared; in addition, samples of serum from (*a*) a normal individual or a pooled specimen from several persons and (*b*) the patient are obtained. Equal volumes of organism emulsion, leucocytes, and serum, are then mixed in capillary tubes, the serum employed in the one tube being the normal specimen, in the other that from the patient. After incubation at 37° C. for fifteen minutes, films are made from the mixtures, and these are stained. The number of cocci contained within 50 or 100 polymorphonuclear leucocytes in each case is then counted. The ratio

$$\frac{\text{Number of cocci ingested by 50 leucocytes with patient's serum}}{\text{Number of cocci ingested by 50 leucocytes with normal serum}}$$

is termed the *opsonic index*, and has been taken as a measure of the patient's immunity toward the organism in question. A persistently low index for a given organism indicates a lack of resistance such as predisposes to the occurrence of infection. Where a localized lesion exists—*e.g.*, an abscess connected with bone—if the patient's serum has a normal index for *Staphylococcus aureus* and a subnormal index for the tubercle bacillus, then the latter is in all probability the causative agent. The underlying hypothesis is that a specific depression of resistance toward a particular organism occurs. Such is not invariably the case, however, as infection with one organism (*M. melitensis*) may cause a fall in the opsonic index for another (*B. tuberculosis*). On the other hand, a supernormal index for a given organism indicates that an immunity response to the infecting organism has occurred, and hence is of diagnostic value as indicating the nature of the infection; more frequent, however, than a permanently elevated index is a fluctuating index. An explanation of this phenomenon is afforded by observations on the opsonic power of the serum during the course of preventive inoculation—*e.g.*, with *B. typhosus*, or of treatment with vaccines. An injection of antigen leads to the absorption of a certain amount of opsonin, and hence to a fall of the index—*negative phase*. This is succeeded by increased immunity, as shown by an elevation of the index—*positive phase*. (If the injections are not given at suitable intervals or in proper amounts, a negative phase may be accentuated or prolonged—results which are undesirable.) Accordingly, a fluctuating index in a case of suspected infection is evidence that a series of auto-inoculations with consequent positive and negative phases is occurring. Stress has been laid on the value of this phenomenon for the diagnosis of active tubercular infection. The occurrence of these phases after inocula-

tion is, of course, a feature connected with all forms of antibody formation. The practical value of the opsonic index depends on the question whether or not the fluctuations which are held to be of diagnostic import are well outside the margin of probable error with the method employed. On statistical grounds, doubt attaches to the significance of small variations in the index (Greenwood and White, etc.).

There is a marked difference between the opsonins of normal and of immune sera. Dean and others have found that opsonin may still be present in an immune serum after heating at 55° C. Muir and Martin have shown that the thermostable immune opsonins (bacteriotropins of Neufeld) have all the characteristics of immune antibodies. On the other hand, they found that a normal serum is deprived of its opsonic action for a given organism by treatment with other organisms. In addition, the various substances and combinations of substances which absorb complement also deprive normal serum of its opsonin, whereas immune opsonin is not affected. Accordingly, the action of the thermolabile opsonin of normal serum depends on complement, and lacks the high degree of specificity which characterizes immune opsonins. The opsonic immune body differs from bactericidal immune bodies, since the former can produce its effect without the aid of complement, whereas the latter is without apparent effect by itself. In an unheated immune serum both normal complement opsonin and also opsonic and other immune antibodies are present; but it is not determined whether in general there is merely a summation of effects, or whether immune body augments phagocytic action by leading to the combination of a further amount of complement opsonin. In one instance Browning demonstrated the production of opsonic effect by the combined action of immune body and complement; thus, staphylococci were opsonized when treated first of all with immune body and then with complement, but when the order of treatment was reversed the opsonizing effect did not occur. Organisms either in the living or the dead state are susceptible to the opsonizing action of serum.

### *Agglutination—Precipitation.*

Gruber and Durham, in the course of investigations on the Pfeiffer phenomenon *in vitro*, observed that the addition of the corresponding antiserum to uniform emulsions of *B. typhosus* and *V. choleræ* caused the organisms to become agglutinated into clumps. The bodies in the serum which produce this effect are termed *agglutinins*. Widal and Grünbaum found that the serum in cases of enteric fever at a very early stage of the disease (the end of the first week) acquired the specific property of agglutinating the typhoid bacillus, a property which is of very great practical value in the diagnosis of infections with *B. typhosus* and other

organisms. Charrin and Roger had observed much earlier that, when *B. pyocyaneus* was grown in the serum of an animal immunized with this organism, the growth formed a deposit at the foot of the vessel; whereas in normal serum the growth formed a uniform turbidity. Both motile and non-motile organisms are capable of being agglutinated. In the case of the former the abolition of motility may or may not be a marked feature preliminary to the occurrence of clumping. The clumps are at first discernible only with the microscope, but later they become visible to the naked eye. Thus, when a powerful agglutinating serum in suitable amount is added to a bacterial emulsion in a test-tube, the agglutinated organisms become deposited at the foot of the tube, leaving the supernatant fluid clear (*sedimentation*); while the emulsion to which an equal amount of normal serum has been added remains uniformly turbid. Agglutinating antisera are obtained by injecting animals with living or dead bacteria, preferably intravenously. Certain organisms give rise to antisera with marked agglutinating properties—*e.g.*, *B. typhosus* and *V. cholerœ*. Thus, after several intravenous injections of dead *B. typhosus* into a rabbit, its serum may agglutinate that organism in a dilution of 1 : 4,000 to 1 : 10,000. In the case of other bacteria—*e.g.*, staphylococci—the antiserum does not possess a marked agglutinating action. The process of agglutination depends on the interaction of two factors—the agglutinin and the agglutinable substance—and a modification of either may affect the result; accordingly, each of these is best considered by itself.

**Agglutinins.**—These in general do not require the co-operation of complement in order to produce their effect (see p. 162). They resist heating at 55° C., but in some cases they may be destroyed at temperatures slightly above this. They do not dialyze, and they are retained to some extent by bacterial filters. Agglutination occurs best at, or slightly above, 37° C. Two phases may be distinguished in the action of agglutinins: (1) the binding of the agglutinin by the bacteria, and (2) the occurrence of clumping. Bordet showed that in the absence of salts bacteria did not clump, although they bound the agglutinin; on the addition of traces of NaCl or other salts or sugar (Friedberger) agglutination occurred. Eisenberg and Volk and others found that antisera which have lost their agglutinating action as the result of heating at 70° to 75° C., or in the course of time, affect the bacteria in such a way that, if after treatment with the inactive serum, the organisms are then placed in contact with a powerfully agglutinating serum, they fail to clump. The inactive serum has rendered the bacilli inagglutinable, and has also prevented them from combining with the agglutinin. These results have led to the view that agglutinins are, in Ehrlich's terminology, "receptors of the second order," possessing a haptophore and a zymotoxic group. The inactivated sera are supposed

to contain agglutinin molecules in which the zymotoxic groups have been destroyed, but the haptophore groups persist—*agglutinoids*. The latter act by plugging up the combining groups of the bacteria, so that the active agglutinin cannot be fixed. Agglutination is produced by an optimum amount of antiserum. If a greater amount of serum than the optimum is present, agglutination may fail to occur. The inhibition of agglutination produced by too high a concentration of serum has been termed the *zone phenomenon*. Similar effects have been observed in precipitation reactions between colloids. Dreyer and Jex-Blake have found that, with a serum in which the agglutinin has been much damaged by heat, there may be only a slight zone phenomenon, whereas a marked zone may occur when no weakening has resulted from the heating. If the weakening of agglutinating power consequent on heating were due to the formation of agglutinoid, one would expect the result to be exactly the opposite of that observed. The question of the existence of agglutinoids is very complex, and has not yet been satisfactorily settled. The agglutinating action cannot be restored by any procedure, such as the addition of complement, to the inactivated sera. Agglutinin is used up in the process of agglutination; it enters into a fairly firm combination with the bacteria, and many times the amount necessary to cause agglutination may be fixed. Müller has shown that the agglutinins of a serum are not homogeneous, since molecules with varying degrees of combining affinity can be distinguished. Agglutinins are specific in the sense already described. Thus, the antiserum to a given organism may agglutinate to some extent other bacteria belonging to the same group. This *group-reaction* can in general be distinguished from the main reaction by the fact that the allied organisms require a greater concentration of serum to agglutinate them than do the homologous bacteria. A further method of differentiation is *Castellani's reaction*, which depends on the fact that the homologous organism will remove all the agglutinin from an antiserum, whereas allied bacteria will remove only the group agglutinins. If an antiserum on treatment with an emulsion of bacterium A is deprived of its agglutinating action for both bacterium A and bacterium B, but if after treatment with bacterium B the serum is deprived only of its agglutinating action for B, and still agglutinates A, then A is the homologous bacterium in response to which the antiserum has been developed, whereas B is an allied organism which has certain receptors in common with A.

*Agglutinable Substance, or Agglutinogen.*—Bacteria are agglutinated both in the living and the dead state. When organisms—*e.g.*, *B. coli*—are heated at 65° to 70° C., they may lose the faculty of becoming agglutinated, although retaining their power of fixing the agglutinin. In certain cases a greater degree of heat may restore the agglutinability (Dreyer and Jex-Blake). A given

bacterium may contain several agglutinogens. Joos has differentiated in *B. typhosus* two agglutinogens which differ in their resistance to heat. A variety of conditions may affect the agglutinability of a given strain of organisms. Thus, organisms recently isolated from the body—*e.g.*, *B. typhosus*—are insusceptible to agglutination; after repeated subculture they become readily agglutinated. This change does not appear to depend on alterations in virulence. Müller produced a similar *serum-resistant strain* of *B. typhosus* by growing the bacilli in bouillon containing anti-typhoid serum. When the bacilli had become inagglutinable, they were found to have practically lost the property of absorbing agglutinin. The nature of the culture medium may also have an effect; *e.g.*, *B. typhosus* is rendered inagglutinable by growth on media containing malachite green. Agglutination of bacteria does not damage their power of proliferation, but they may show morphological alterations; *e.g.*, typhoid bacilli in the presence of agglutinating serum grow in long chains—the so-called *thread reaction*.

*Hæmagglutination.*—Certain immune sera obtained by injecting blood-corpuscles cause agglutination of the red cells. The hæm-agglutinins resist heating at 55° C.; they are also found in normal sera. Landsteiner and Reich found that normal agglutinins were less specific and much more easily dissociated from the corpuscles by heating than immune agglutinins. The agglutinins absorbed from normal serum by one species of blood, and then dissociated by heating, were found to cause agglutination of the red corpuscles of other species. The action of complement as agglutinin was demonstrated by Muir and Browning. Ox's red corpuscles sensitized with immune body from the rabbit become firmly agglutinated on the addition of fresh ox serum; ox serum heated at 55° C. has no action. Ox serum appears to contain also a thermostable substance, the *conglutinin* of Bordet and Streng, which in the presence of complement leads to agglutination of sensitized blood-corpuseles.

**Precipitins.**—Soon after the discovery of agglutinins Kraus found that the corresponding antiserum, when added to filtrates of cultures of *B. typhosus*, *V. cholerœ*, etc., caused cloudiness to appear, and later on a precipitate. The body in the immune serum which produces this effect is called a "precipitin." Bacterial precipitation is of importance on account of the light which it throws on the process of agglutination. *Serum Precipitins.*—When the serum of species A (the *precipitinogen*) is repeatedly injected into an animal of species B, there appears in the serum of the latter a precipitin for the serum of A. When the antiserum is added to the precipitinogen in suitable proportions, a cloudiness or precipitate is formed. This reaction is very delicate, and a definite cloudiness may be observed with 0·001 c.c. of serum or less. The precipitin reaction is specific in the sense described above. An antiserum reacts most markedly with the serum of

the species employed for immunization, and may react to a slight extent with the sera of allied species. Thus, antihuman serum gives the greatest reaction with human serum, and a slight reaction with monkeys' sera, especially that of anthropoid apes; with the sera of other animals no reaction is given. Consequently the precipitin reaction has been employed as a means of determining zoological relationships, and for distinguishing human blood from that of other species for forensic purposes. Blood-stains many years old may thus be recognized. Rabbits are usually employed for the production of precipitins. As in the case of agglutination, zone phenomena occur. An antiserum which has been heated at 75° C. prevents the formation of precipitum in a mixture of serum and antiserum. Welch and Chapman have shown that this inhibitory effect cannot be adequately explained by the theory that precipitoids are formed by heating, but that it is due to the specific solvent action which the heated antiserum exerts on the precipitate. They have also demonstrated the important fact that the precipitum is chiefly composed of constituents of the antiserum, and not of the precipitinogen. The mixture of serum and antiserum has the property of absorbing complement. Deviation of complement is a much more delicate reaction than precipitation, since, as Muir and Martin have shown, it is often possible by its means to demonstrate a tenth to a hundredth of the smallest amount of serum which will give a perceptible precipitate. It is specific within the same limits as precipitation. The fact that an antiserum obtained by immunizing with any organ of a given animal species does not contain antibodies for the serum of that species is important from the point of view of specificity (Fleischmann and Davidsohn). Antisera obtained by immunizing with serum, in addition to precipitating and complement-deviating capacities, possess other properties. Thus, an antiserum to the serum of species A contains an anti-immune body antagonistic to all the immune bodies which can be obtained by immunizing animals of species A (Bordet). This may explain the comparatively short duration of passive immunity where the antiserum injected is derived from a different species.

The nature of the process of agglutination has not yet been clearly determined. Originally it was supposed that the surface of the bacterium became sticky (Gruber and Durham), and that the flagella were involved (Dineur). There is no direct evidence in favour of the former view, and the latter is not essential, as many non-flagellated organisms show agglutination. Bordet regards the agglutinin as altering the molecular attraction of the bacteria. Again, agglutination has been regarded as practically identical with the precipitation of bacterial proteins, the precipitable material not being situated in the fluid, but in the bacterial bodies (Paltauf). It may be said in general that the affinity of agglutinin

for the bacteria is of a chemical nature, and that when combination has occurred the subsequent processes are of the nature of colloid reactions which depend on the constitution of the surrounding medium.

### *Deviation of Complement.*

A large number of antisera contain antibodies which, in conjunction with the corresponding antigens, have the property of absorbing complement (*Bordet-Gengou reaction*). Among such antigens are bacteria, red blood-corpuscles and other tissue cells, serum and other protein bodies. Certain other antigens in combination with their corresponding antibodies have no affinity for complement—*e.g.*, diphtheria toxin and antitoxin. The method of demonstrating complement deviation is as follows: Antigen, antibody, and complement-containing serum, are mixed, and the mixture is allowed to stand for some time, usually at 37° C.; then the test amount of suspension of red blood-corpuscles sensitized with immune body (the hæmolytic system) is added, and the mixture is again incubated at 37° C. The absence of hæmolysis of the test corpuscles indicates that no free complement is present—that is to say, the complement has been absorbed or deviated in the first stage of the reaction. As the hæmolytic system, ox or sheep blood sensitized with immune body from the rabbit is usually employed. Fresh guinea-pig's serum is used as the source of complement, since it contains in great concentration complement molecules which have a high combining affinity, and at the same time are actively hæmolytic for the test corpuscles. The complement deviation reaction is not qualitative, but strictly quantitative, the amount of complement absorbed being measured in hæmolytic doses. Varying amounts of complement-containing serum are added to a series of tubes, each of which contains the standard amount of the mixture of antigen and antibody. In this way it is possible to determine exactly how much complement is absorbed, by noting in which tube the first trace of lysis occurs, and in which there is complete lysis of the test corpuscles. At the same time, by way of control, the effect on complement of antigen and of antibody, each by itself, is estimated. When a true deviation reaction occurs, the amount of complement absorbed by the mixture of antigen and antibody is greatly in excess of the sum of the amounts absorbed by each separately. Accordingly, it is clear that sensitized corpuscles constitute a test for complement; the occurrence of hæmolysis indicates the presence of free complement, but if the corpuscles remain intact there is no free complement. The following is an example of the procedure which is adopted in order to determine whether a certain antigen is present: If the presence of human serum is suspected, the antibody corresponding with the supposed antigen is added—*i.e.*, antihuman serum along with

complement; then, after allowing time for combination, the effect of the mixture is tested on the hæmolytic system. If no hæmolysis occurs, the complement has been absorbed, hence the antigen present corresponds with the antibody; if the corresponding antigen is not present, the complement remains free and lysis of the test corpuscles takes place. In similar fashion, the presence of a suspected antibody is tested for by adding the known antigen, and then observing if the combination absorbs complement. The amounts of antigen and antibody must bear a certain ratio to each other in order that complement fixation may occur; an excess of either reagent, especially the antigen, may prevent the deviation. The reaction is specific in the sense explained above. The complement deviation reaction has been applied practically in the identification of bacteria—*e.g.*, the identification of *B. typhosus* in mixed cultures from fæces (Dean), and in the identification of blood-stains. The most important application of the method is *Wassermann's syphilis reaction*, which gives a positive result in 75 per cent. of all cases of active syphilis and in 50 per cent. of latent cases. It depends on the fact that syphilitic serum which has been heated at 55° C., when mixed with an emulsion of certain lipoids—especially a combination of liver lecithin with cholesterin (Browning, Cruickshank, and Mackenzie)—causes deviation of complement. Sera in other diseases, with the exception of tubercular leprosy and yaws, do not give the reaction. The reaction is analogous to that which occurs with the combination of antigen and antibody; but the reacting bodies of the syphilitic serum are not antibodies to the *Spirochæta pallida*, and the lipoids are not antigens in the true sense of the term. Recent investigations have shown that in these reactions the whole complement is not necessarily used up, but merely the middle piece.

### *The Site of Formation of Antibodies.*

Evidence regarding the site of formation of antibodies is somewhat deficient. Antibodies may be formed locally, without the body in general participating. Thus, Römer found that, after treating one eye of a rabbit with a solution of abrin, this eye alone became immune, and the ground-up cornea neutralized abrin when mixed with it *in vitro*. The organs which are rich in leucocytes (bone marrow, spleen, lymph glands) seem to take an active part in the formation of antibodies, as they appear first in these organs. Probably endothelium in general is actively concerned.

### *The Relationships of the Various Antibodies of an Antiserum to One Another.*

As has been seen, an antibacterial or anticellular immune serum may possess a variety of actions, each of which has been referred to as if it were due to a separate substance—opsonin, agglutinin,

immune body, etc. The question, therefore, arises as to whether the different phenomena are really due to separate antibodies, developed in response to different antigens contained in the bacteria or cells, or whether they are all manifestations of a single antisubstance. It is not possible to settle the point definitely so long as the antibodies cannot be isolated in the pure state ; but the evidence points to their being independent in many instances. Thus, the functions of a given serum can vary independently ; *e.g.*, Pfeiffer and Kolle found that in the human subject, after injections of *V. choleræ*, the serum acquired both agglutinating and bacteriolytic properties, but after some months the former had disappeared, the latter, however, remained well marked. Also, by treating an immune serum with the corresponding bacteria, all the agglutinin may be removed, but the treated serum may retain its power of conferring passive immunity. The independence of the bactericidal, opsonic, and agglutinating properties of immune sera has been clearly demonstrated (Muir and Martin, Neufeld and Hühne).

### *The Therapeutic Application of Antibacterial Sera.*

The treatment of infections by antibacterial sera has in general not been attended by great success. A number of reasons may account for the failure. As is the case in cholera, the infected subject may succumb to endotoxins liberated from the bacteria. Again, the bactericidal immune bodies of the antiserum require a suitable complement for their action. The infected subject may not possess complement suitable for an immune body derived from a widely different species, or the supply of bactericidal complement may be used up in the course of the infection, although the complement content of the serum, as estimated by hæmolytic tests, is usually increased in the acute stage of infectious diseases (Gunn). In any case, the introduction of a sufficiency of complement to serve the tissues in general is not possible in the human subject. In the case of certain organisms—*e.g.*, streptococci—different strains differ markedly in their receptors, so that an antiserum obtained by immunizing with one strain does not act on another. To obviate this difficulty in treatment, *polyvalent sera* have been prepared by immunizing with a mixture of several different strains. Promising results have been obtained in the treatment of cerebrospinal meningitis by Flexner and Jobling's antimeningococcus serum, the use of which has reduced the death-rate from 70-80 to 30 per cent. In this disease the chief site of infection is the cerebrospinal system, and the antiserum is injected intraspinally. The mode of action is not clearly determined ; the meningococci are disposed of, apparently, by phagocytosis, since complement which is necessary for direct bactericidal action is absent. A rational procedure in the treatment of this disease was adopted by Mackenzie

and Martin, who injected intraspinally the fresh serum of a recovered case or of the patient himself; such serum has a marked bactericidal and opsonic action on meningococci, due to the presence of specific antibodies along with complement. In all cases it is essential to employ a sufficient dose of antiserum.

### Theories regarding the Nature of Acquired Immunity.

Several of the theories advanced at an early date to explain the nature of immunity have been rendered untenable by subsequent observations which have been found to be of general application. Thus, the *theory of exhaustion* (Pasteur, Klebs) was based on the assumption that the tissues contained only a fixed amount of substances necessary for the growth of a given organism. When these bodies were exhausted, the organisms died out owing to the lack of material essential for their nutrition. This view was disproved by the fact that the corresponding organisms grow equally well on the tissues of an immune and of a susceptible animal. According to the *theory of retention* (Chauveau), organisms produced substances in the body inimical to their own growth; the accumulation of these derivatives of the bacteria ultimately caused their destruction. This view in its latest form represented antitoxins as modified toxins (Buchner); but this is disproved by the fact that the amount of antitoxin developed is capable of neutralizing many times the dose of toxin introduced. The theory as a whole is controverted by the facts of passive immunity. The *phagocytic* and the *humoral* theories, respectively, have been highly elaborated by Metchnikoff and by Ehrlich. These theories do not apply to precisely the same series of phenomena, but they both agree in referring the condition of immunity ultimately to processes of cell metabolism. They are to a great extent supplementary, and in combination explain a very large number of the facts of immunity. There are, however, certain phenomena which in the present state of knowledge cannot be explained by any theory.

**Metchnikoff's theory of phagocytosis** was the outcome of his investigations on the processes whereby animal organisms dispose of material foreign to or no longer required by them. He found that just as amœbæ have the property of ingesting bacteria and other small particles, which are then acted on by intracellular secretions with a digestive action and are rendered fit for assimilation as food, so also the capacity for ingesting particles is possessed by many cells of the tissues of higher animals, which he therefore termed *phagocytes*. This function in the mammalia is exercised especially by the leucocytes and endothelial cells. On investigating the nature of inflammation, Metchnikoff found that the accumulation of leucocytes in the inflamed area was a constant phenomenon. Hence he concluded that the activity of the leucocytes was the

essential feature of inflammation. Thus, when a moderately susceptible animal was inoculated locally with a culture of a given bacterium, there occurred an accumulation of leucocytes, and the organisms were ingested by them. The living active bacteria after being ingested ultimately showed changes in their structure, which indicated that they had been killed. The attraction of leucocytes by the bacteria was termed *positive chemotaxis*. On the other hand, when a highly susceptible animal was inoculated, the leucocytes, instead of being attracted, were repelled—*negative chemotaxis*—which is attributed by Bail to the action of aggressines (see p. 142), and the organisms, instead of being killed off, showed progressive proliferation, and finally invaded the blood-stream and, multiplying there, caused septicæmia. When a susceptible animal was rendered insusceptible by immunization, the leucocytes were attracted instead of being repelled; thus negative was converted into positive chemotaxis, and phagocytosis occurred. Accordingly, Metchnikoff concluded that phagocytosis constituted the essence of immunity both natural and acquired. Phagocytes in the human subject are divided into two classes—*microphages* (the polymorphonuclear, finely granular leucocytes of the blood), which ingest bacteria; and *macrophages* (large hyaline leucocytes, endothelial and young connective-tissue cells, etc.), which take up protozoa and various formed tissue elements. The ingested particles are digested by means of ferments, microcytase and macrocytase respectively. When the cells are damaged, these ferments, which are intracellular under normal conditions, by the process of *phagolysis* become shed into the surrounding fluid, and constitute alexin or complement. The bactericidal action of normal serum is thus due to the presence of microcytase liberated from the microphages which have been damaged in the process of coagulation of the blood. Metchnikoff's explanation of the properties of an immune antibacterial serum is that the immune bodies are fixed by the bacteria; these *fixateurs* are auxiliary ferments (*ferments adjuvants*) which aid the action of the alexin in much the same way as enterokinase aids trypsin. Fixateurs are formed in excess as the result of immunization, and they may appear free in the serum. Bacteria which have fixed the immune body may be digested within the phagocytes or may undergo extracellular lysis, but the latter process does not occur unless cytase has been liberated as the result of phagolysis. Thus, the extracellular destruction of organisms in the peritoneum of an immunized guinea-pig (Pfeiffer's phenomenon) is regarded as being due to the presence in the peritoneal fluid of microcytase consequent on phagolysis. Metchnikoff points out in this connection that extracellular bacteriolysis does not account for the destruction of all the organisms introduced into the peritoneum, since bacteria can always be found inside phagocytes situated on the omentum many hours after the Pfeiffer

phenomenon has come to an end, and when specimens of fluid withdrawn from the peritoneum by a capillary tube are apparently sterile. Immune bodies are probably formed within the leucocytes, since the leucocyte-forming organs are specially rich in these substances, the bactericidal immune bodies being formed in the polymorphonuclear cells, and the cytolytic antibodies in the mononuclear cells. When there is marked active immunity against a given bacterium, and the serum does not possess bactericidal properties, this is to be explained by the fixateur being retained within the leucocytes. Several difficulties beset this theory: (1) Phagocytosis does not necessarily imply the existence of immunity; thus, in an acute meningococcus infection the cocci are found within the leucocytes mainly, and yet death may ensue. (2) There is no conclusive evidence that complement is absent from the blood-plasma under normal conditions. (3) The bactericidal bodies which have been extracted from leucocytes do not correspond in their characters with those present in the serum. (4) It has not been possible to demonstrate distinctive differences between the leucocytes of immune and of susceptible animals by opsonic experiments *in vitro*. With regard to immunity to toxins, Metchnikoff holds that, in addition to the direct neutralization of toxin by antitoxin, acquired resistance of the cells is an important factor. Metchnikoff's views relegate the functions of the tissue fluids to a comparatively subordinate position for reasons which do not appear to rest on a well-established basis, but they have proved of the highest value in directing attention to the extremely important part which phagocytosis undoubtedly plays in immunity.

**Ehrlich's side-chain theory** is concerned chiefly with the origin and properties of the antibodies present in the tissue fluids of immune animals. These substances are regarded as products of cellular activity which are secreted into the blood-plasma and other fluids. An outline of the theory, so far as antitoxin production is concerned, has already been given, and the other types of antibodies are held to be produced in conformity with the same laws. It is supposed that all antigens belong to the same class of substances as those which serve as foodstuffs for the cells. In order to be able to assimilate such bodies, the protoplasm molecule is provided with side-chains of atom groups, or receptors, which are attached to, and elaborated by, the central nucleus (*Leistungskern*); for each different type of molecule which is to be anchored by the protoplasm there must be a separate type of receptor with chemically distinct configuration. Thus Ehrlich conceives specificity as being purely due to distinctive chemical structure. The combination of antigen with the cell receptor is firm, and the receptor is thus rendered useless for further functional purposes, and requires to be replaced by another similar receptor, which is elaborated by the central nucleus. In the process of immunization, the specific receptors which are

manufactured greatly exceed in number the antigen molecules which have been introduced. The excess of receptors is set free from the cells into the blood-plasma, and there they act as antibodies in the manner already described. Receptors are distinguished as belonging to three groups: (1) of the first order—*e.g.*, antitoxins—which possess only one combining group for anchoring a relatively simple molecule; (2) of the second order—*e.g.*, agglutinins—provided with a combining group and a zymotoxic group, the latter producing some physical alteration in the molecule after combination has occurred; (3) of the third order (amboceptors)—*e.g.*, bacterial immune bodies—which possess two combining groups, one of which anchors the food molecule and the other fixes complement, which by its ferment-like action breaks down the molecule for purposes of assimilation. This last type of antibody comes into operation in the case of relatively large molecules.

While Ehrlich's theory offers the most satisfactory explanation for a very large number of phenomena, certain difficulties have arisen which must be solved by future investigation. These will be shortly referred to here: (1) There is not sufficient evidence for the belief that the molecules which act as antigens are closely similar to the foodstuffs of the cells. As a matter of fact, the animal body seems to prevent strictly the entrance into its circulation of complex molecules with specificity other than its own. Thus, the immunity reaction would represent rather a response to the introduction of foreign proteid material than a physiological process. (2) The numerical disproportion between the small quantity of toxin introduced into an animal and the large amount of antitoxin which is produced in response (in Knorr's experiment the antitoxin produced was sufficient to neutralize 100,000 times the immunizing dose of tetanus antitoxin) has led Kassowitz to conclude that a single molecule of toxin may successively combine with a molecule of protoplasm, and then decompose it, thus becoming free to act similarly on a series of molecules. Muir and M'Nee's experiments showing the dissociation of hæmolytic immune body *in vivo* furnish a strong support to this view. (3) The hypothesis that for every molecule that can act as an antigen in a given animal there must be present in some of its tissues a specific receptor preformed predicates the existence of a vast number of receptors which are in general never called into use. This consideration, as well as the facts that (*a*) the curative action of antitoxin must depend on "free receptors" in the antitoxic serum possessing a greater affinity for toxin than the "sessile receptors" of the tissues, since the antitoxin neutralizes toxin which has already entered into combination, and (*b*) natural antibodies manifest less specific affinities than immune anti-substances, all suggest that the original receptors in the cells with which the antigens at first combine may be comparatively undifferentiated, and that the very high grade of

specificity shown by the immune antibodies is, in part at least, a result of the immunizing process (Landsteiner, Kassowitz). (4) Meyer and Ransome found that when an animal actively immunized against tetanus, and with antitoxin in its blood, received an injection of tetanus antitoxin into a motor nerve fatal tetanus ensued, although subcutaneous or intravenous injections of toxin were without effect. This observation is difficult to reconcile with the view that antitoxin is necessarily formed by the cells which combine with, and are susceptible to, the action of the toxin.

The protective and the curative effects of an immune serum afford a conclusive proof of the important part which the body fluids play in immunity. Of the various immunity reactions which have been investigated, there can be no doubt that antitoxic, bactericidal, and opsonic effects occur in the animal body, and directly contribute to the production of immunity (agglutination and precipitation are probably to be regarded merely as *in vitro* phenomena). In a given instance one particular form of reaction may preponderate; thus, immunity to diphtheria is essentially antitoxic, and to *V. cholerœ* bactericidal. But in general the reactions supplement each other; *e.g.*, when *B. typhosus* is introduced into the peritoneum of an immunized guinea-pig, the majority of the organisms are killed outside the cells, but a proportion are taken up by leucocytes and then digested. Thus, immunity results from the operation of a number of factors, many of which can be precisely measured, but no one of which can be relied upon to afford an accurate index of the actual immunity; *e.g.*, a serum may possess great agglutinating power, and yet have no protective action against infection. An immune serum, however, may not possess any of the above-mentioned properties in a higher degree than normal serum, and yet it may have a very powerful action in conferring passive immunity—*e.g.*, anti-anthrax serum. Virulent anthrax bacilli may remain alive for over a week in the circulation of actively immune animals; hence it might appear as if the serum were antitoxic, although no toxin formation can be demonstrated in the case of *B. anthracis*. Such results suggest that there are manifestations of antibody action which remain to be discovered. Again, when it is found that active immunity has been acquired, but that anti-substances cannot be detected in the serum of the immune individual, the conclusion must be drawn that alterations have occurred in the cells. An example of such a condition is the immunity to reinfection which exists for years after typhoid fever, at a time when protective substances have practically disappeared from the blood.

### *Alterations in the Reacting Power of Cells resulting from Immunization.*

Previous immunization alters both the rate and the mode of reaction to a subsequent inoculation. Von Dungern found that rabbits previously immunized with a given protein, and from whose serum all precipitin had disappeared, when reinjected with the same dose of the protein developed precipitin much more rapidly and more abundantly than after the previous injections. Such capacity for increased reaction may explain insusceptibility to reinfection when protective substances are no longer present in the blood. Again, Dreyer observed that an injection of dead staphylococci into rabbits previously immunized with *B. coli* led to a marked increase of the agglutinating power of the serum for *B. coli*. Cellular alterations, apart from the power of producing antibodies, have not yet been investigated fully. Some facts, however, have been ascertained. Thus, reaction with an antigen may produce a marked alteration in the susceptibility of cells. Acquired insusceptibility is frequently local; successful inoculation of a rabbit's cornea with vaccinia results in insusceptibility to re-inoculation, which is limited to that cornea. An immunized animal also may be insusceptible to toxin, although little or no antitoxin can be demonstrated in its blood. Increased susceptibility as the result of immunization is exemplified by the *phenomenon of Kretz*, who observed that a mixture of toxin with sufficient antitoxin to produce no effect on normal animals causes a reaction in animals which have previously been immunized with the toxin. Similarly, an immunized animal may succumb to a dose of toxin which could be neutralized many times over by the antitoxin in its blood. These phenomena have been attributed, however, by Friedberger to anaphylaxis (p. 177).

### Resistance and Natural Immunity.

*Resistance* may theoretically be differentiated from natural immunity by the fact that the former is not specific, the latter specific; but actually it is difficult in many instances to make the distinction. The theories of immunity which have gained acceptance agree in referring the condition ultimately to processes of cell metabolism. It appears, therefore, that whatever favours cell nutrition in general will tend to increase those functions on which immunity depends. On the other hand, conditions which lead to a localized diminution of resistance, such as trauma, may enable infective agents to obtain a hold on the tissues. Conversely, an increased blood-supply (*e.g.*, Bier's treatment), or an accumulation of leucocytes, may lead to increased local resistance to a variety

of infective agents, just as, for example, an injection of bouillon increases the resistance of the peritoneum to subsequent infection. The general resistance is diminished by starvation, over-exertion, chronic alcoholic poisoning, or chilling, and is increased by whatever benefits the general health. Resistance also depends to a marked extent on peculiarities of the individual.

**Natural Immunity**—(*a*) *Insusceptibility to Infection.*—Natural immunity usually comes into play in preventing the occurrence of infection. Absolute susceptibility in an animal is a very rare condition; that is to say, if the dose of the infective agents is not too large, they can be dealt with by the normal tissues immediately, and disease does not develop. As has been seen, normal serum possesses bactericidal and opsonic action for various bacteria, and doubtless these properties of the tissue fluids, together with the capacity of the cells to destroy ingested bacteria, account for immunity, even although the processes may not occur in exactly parallel fashion *in vivo* and *in vitro*. It has not been possible to determine whether on the analogy of an immune serum the bactericidal action of normal serum is always due to the co-operation of complement with a natural immune body, or whether alexin may act alone; it has already been shown that only a small proportion of the complement is effective in this respect. In certain instances normal immune bodies have been found—*e.g.*, that for *B. anthracis* in dog's serum. Great variations in susceptibility are manifested by different races and species. *Race immunity* is strikingly shown in the case of anthrax in sheep; ordinary sheep are highly susceptible, whereas the Algerian race shows marked immunity to infection. *Species immunity* also varies greatly in the case of anthrax. Dogs, rats, and fowls can only be infected with difficulty by large doses of anthrax bacilli, and are thus practically immune, whereas mice, guinea-pigs, and rabbits, are extremely susceptible. A great amount of investigation has been carried out in the attempt to explain these differences. Gruber and Futaki's work is the most extensive, and their results have shown that (1) *in vivo* and *in vitro* phenomena do not necessarily correspond, and (2) the causes of immunity vary in different animals. Thus, rabbits are extremely susceptible to subcutaneous infection with anthrax, and, corresponding with this, the cell-free fluid obtained by inserting a wad of cotton-wool under the skin is almost devoid of bactericidal action, whereas lymph similarly got from the fowl is extremely active. The explanation is that the leucocytes of the fowl contain bactericidal bodies in greater abundance, and give them off more readily than do those of the rabbit. The bactericidal action of rabbit's and rat's serum *in vitro* is due to bodies derived from the blood-platelets; the blood-plasma, on the other hand, is not bactericidal, since these products of the platelets are not set free into the plasma. The platelets of the fowl and the guinea-

pig do not contain bactericidal bodies. The high body temperature of the fowl is also unfavourable to the anthrax bacillus. Such results indicate how complicated the conditions may be which operate together to produce a state of insusceptibility. *Passive transference of natural immunity* has been effected. Mice are extremely susceptible to infection with *Trypanosoma Brucei*, whereas the human subject is immune, and human serum heated at 55° C., when injected into mice, protects them against infection.

*Athreptic Immunity.*—Ehrlich observed that a virulent mouse tumour, when introduced into a rat, grew for a certain time. If the tumour in the rat, at the height of its growth, was transferred into a second rat, it failed to grow; but if it was transferred to a mouse growth took place, and a second rat could then be successfully inoculated from the mouse. Ehrlich's explanation of this phenomenon was that the tissues of the mouse contain a substance which rat's tissues lack, and which is essential for the growth of mouse tumour; when an inoculation is made from mouse to rat, sufficient of this growth-stuff is transferred in the fragment of tumour to permit of a certain degree of proliferation. Growth in a second rat fails simply from lack of the essential foodstuff (*athrepsy*). Natural immunity to bacteria may have a similar explanation in some cases.

(*b*) *Insusceptibility to Toxins.*—There is as yet no complete solution of the problem why one animal should be much more susceptible to a given poison than another. The dose must in every case, of course, exceed a certain minimum before toxic effects follow. The site of application of the toxin is of importance; thus, diphtheria and tetanus toxins produce no effect when taken into the alimentary canal, whereas the toxin of *B. botulinus* acts by absorption from the bowel. In accordance with Ehrlich's view as to the constitution of toxin, insusceptibility may be due to a variety of conditions: (1) Antitoxin may be present in the blood normally; *e.g.*, human serum usually contains diphtheria antitoxin. The absence of any etiological or teleological explanation for the existence of normal anti-substances in serum is well illustrated by the presence in rabbit's serum of an antitoxin to the toxic action of echinus spermatozoa for sea-star ova. (2) An animal's tissues may have no receptors which fit the haptophore group of the toxin; thus, tetanus toxin injected into the turtle remains free indefinitely in the body fluids. Sachs demonstrated *in vitro* that arachnolysin is fixed by susceptible blood-corpuscles, but not by insusceptible blood. (3) The toxin may be fixed, but the cells with which it has combined may be insusceptible to the action of the toxophore group; this is the case with tetanus toxin in the frog's nervous system. The existence of receptors outside the nervous system in organs which are insusceptible to the toxic action explains why the rabbit is much less sensitive to tetanus

toxin injected subcutaneously than when injected into the brain. Muir and Browning have shown that an amount of complement which, when combined with one species of red corpuscles, exerts a powerful toxic action, as shown by the rapid occurrence of hæmolysis, may produce practically no effect when combined with similar receptors in the blood-corpuscles of another species. This fundamental fact, that the molecules of different animals may vary in their sensitiveness to toxic action, has so far received no explanation.

### Immunity and Recovery from Disease.

Infection in the human subject is usually due to a very minute dose of the pathogenic agent, and differs in this respect from most experimental infections; accordingly the normal resistance is an important defensive factor. When this has been overcome the organisms proliferate, and an attack of the disease occurs which very frequently exhibits clinical features distinctive for the particular pathogenic agent concerned, so that a disease may be recognized even when the causal agent is unknown—*e.g.*, scarlet fever. The reduction in general resistance which takes place may predispose to a secondary infection with other organisms, such as the invasion of the tissues by *B. coli* in the course of typhoid fever. During disease organisms are constantly being broken down, and the tissues react to the bacterial products. This reaction is shown by the appearance and accumulation of specific antibodies in the blood-serum. The disease, after lasting a certain time, may come to an end spontaneously. The duration and mode of termination are often characteristic—*e.g.*, in pneumonia. The protective powers acquired by the serum persist for a variable period after convalescence, and there is immunity to reinfection which may last throughout life, as after smallpox, or which may be of comparatively short duration—perhaps not more than some weeks in the case of erysipelas or pneumonia. It is well known that only a proportion of those who have been exposed to infection develop the disease. Of the others whose health has never shown any disturbance, a certain number have, however, been infected. The fact that a *latent infection* has occurred is proved by finding specific reaction bodies in the serum; thus, in the case of exposure to infection with *B. typhosus*, the Widal reaction proves that many more become infected than those who become ill. The body, however, differs markedly in its power of reacting to different pathogenic agents, since in the case of meningococcus infection specific opsonins and agglutinins do not appear in the blood in cases which rapidly recover after an acute onset, the stimulus for antibody formation being furnished only when the disease is of sufficient duration as well as severity (Macgregor). Those who react to the infective agent without manifesting any

disturbance of health obviously possess in a very marked degree the capacity for acquiring immunity. Natural immunity and the capacity for acquiring immunity after infection has occurred should be clearly distinguished, as Brownlee has pointed out. These two properties need not be present in a parallel degree in the same individual. Great natural susceptibility may be accompanied by great capacity for acquiring immunity, as in chicken-pox; again, great natural immunity to glanders on the part of man is associated with incapacity to acquire immunity after infection has occurred. Rinderpest is an example of a disease to which there is great susceptibility, and at the same time very little capacity for acquiring immunity, since almost all oxen exposed to infection contract the disease, and 90 per cent. of those affected die. Natural and acquired immunity are thus not necessarily due to the operation of a similar mechanism. Recovery from a disease does not necessarily imply that the pathogenic agents have all been killed off. As Ehrlich has pointed out, it is necessary to distinguish between *sterilizing* and *non-sterilizing immunity*. In bacterial infections as a rule recovery is associated with complete disappearance of the organisms, but bacteria virulent for other individuals may persist in a subject who is apparently perfectly healthy; thus, after recovery from diphtheria *B. diphtheriæ* may persist in the throat for many months. Similarly, after infection with *B. typhosus* the bacilli may persist in the gall-bladder, and pass in great number into the fæces; at the same time the existence of immunity is proved by the fact that no lesion of the intestine results. In protozoal infections non-sterilizing immunity is the rule; thus, the immunity of native races to malaria is due to a chronic infection acquired in childhood. Syphilitic infection does not die out spontaneously in an infected individual, and it is the existence of latent infection which produces the so-called "immunity to reinoculation." When the spirochætes have been completely killed off by chemotherapeutic agents, susceptibility is very soon re-established. An important factor in the production of non-sterilizing immunity is the power of adaptation possessed by the infecting agent. Franke found that in animals affected with chronic trypanosomiasis the serum possessed trypanocidal action towards parasites of the strain originally employed to produce the infection, although it was without effect on the animal's own trypanosomes—that is to say, the trypanosomes in the animal's body had become immune to the action of its serum. Similar serum-resistant strains have been produced by exposing the parasites to serum *in vitro*. Accordingly, it can well be understood how a condition of equilibrium between parasite and host may come to exist. Any disturbance of the immunity of the host will lead to further manifestations of disease; such recurrences are common in syphilis, and also may occur in chronic bacterial infections—*e.g.*, with *B. typhosus*.

### Supersensitiveness, or Anaphylaxis.

Certain substances of protein nature, when introduced into the animal body in non-toxic doses, produce such changes in reacting power that ultimately a stage is reached after which a further small dose causes toxic effects, and perhaps death. An animal whose mode of reacting has been altered in this manner is said to be in a condition of *supersensitiveness*, or *anaphylaxis*. This state, which is apparently the direct contrary of immunity, must be clearly differentiated from cumulative action, just as toleration of drugs is to be distinguished from immunity. The dose of protein which produces the anaphylactic state, together with that which causes the toxic phenomena, if injected all at one time into a normal animal, produce no toxic effects. Phenomena of supersensitiveness have long been known. Behring, when attempting to immunize guinea-pigs with tetanus toxin, found that repeated minute doses caused supersensitiveness, and the animals died after receiving only one four-hundredth of the amount of toxin required to cause death in a single dose. The earliest example of supersensitiveness which aroused marked attention was Koch's observation of the susceptibility of tubercular patients to tuberculin. The term "anaphylaxis" was in the first instance applied by Richet to the supersensitiveness following repeated injections of a poison derived from actinia, which was called "congestin." Arthus found that, when rabbits received repeated injections of horse serum, a stage was reached at which a further injection given subcutaneously produced marked œdema or necrosis, and when given intravenously caused death, although similar doses were harmless to untreated animals; he termed the alteration in reacting power *allergy*. Active inquiry on the subject, however, dates from the investigations of the *Theobald Smith phenomenon*. Smith observed that guinea-pigs which had received an injection of a neutral mixture of diphtheria toxin with antitoxic serum from the horse died on being injected, after a suitable interval, with normal horse serum. It was found that the toxin was not an essential factor in phenomenon (Otto, Rosenau and Anderson). The *serum disease* was the name given by Von Pirquet and Schick to the phenomena which occur in man after the injection of a foreign serum, such as diphtheria antitoxin; these observers drew attention to the marked differences between the effects of a first and of a subsequent injection.

*The phenomena of serum anaphylaxis in the guinea-pig* will be described in detail, as this is the condition which has been most closely studied experimentally. A sensitizing dose of 0·01 to 0·1 c.c. horse serum is injected subcutaneously (even fifty times the latter amount causes no toxic effect). If ten to fourteen days later 0·2 c.c. of horse serum is injected intravenously, symptoms of

anaphylactic shock supervene. Almost at once the animal becomes restless; then violent convulsions occur; the animal falls on its side; there are a few deep inspiratory movements; but the thorax remains fixed, and death from suffocation takes place about five minutes after the injection. The blood-pressure falls during the attack, the coagulability of the blood is diminished, and there is leucopenia. The heart continues to beat for some time after death. Post mortem the lungs are in a state of very marked emphysema with contracted bronchioles, and the organs show punctiform hæmorrhages. If the second dose of serum is smaller, or if it is injected intraperitoneally, the stage of excitement occurs as described, but is less marked, with only slight convulsive movements, and the animal passes into a state of depression; it lies on its side, and the breathing is shallow. Death may occur in a few hours, or recovery takes place, and the animal may then die in a state of marasmus in some weeks. The feature of this form of attack is the great fall in blood-pressure, and post mortem the organs show congestion and small hæmorrhages.

*The substances which cause supersensitiveness*—anaphylactogens—are proteins or undissociable from proteins—*i.e.*, they belong to the class of antigens. Among the substances toward which supersensitiveness has been developed are bacteria, serum, red blood-corpuscles and other tissue cells, egg-white. In general the protein must be foreign to the animal which is treated. The sensitizing power of protein is destroyed by the digestive juices, hence supersensitiveness characteristically follows the direct or so-called "parenteral" injection into the tissues; but under certain conditions sufficient unaltered protein may be absorbed from the alimentary tract to be effective. Sensitization can be effected by very minute amounts of protein (0·00000005 gramme of crystallized egg-albumin in a guinea-pig). Toxic phenomena are most readily produced in a supersensitive animal by intravenous injection, and the dose which produces a fatal result may be much less than a thousandth part of the amount which produces no effect in a normal animal. Wells produced death in an anaphylactic guinea-pig by 0·0001 gramme crystallized egg-albumin. Rabbits, mice, and dogs, can be rendered supersensitive, but are less susceptible than guinea-pigs. There is no conclusive evidence in favour of the theory that the sensitizing and the toxic action are due to different components of the protein. Besredka's view that the sensitizer was thermostable, while the production of shock depended on a thermolabile body, appears to have neglected the fact that the amount of protein required to produce anaphylactic shock may be a thousand times greater than the sensitizing dose; hence, if both of these functions are diminished to a parallel extent by heating, it may be impossible to inject a sufficient dose of the damaged protein to elicit a reaction in an anaphylactic animal. Anaphylaxis is specific in the same

sense as immunity—that is to say, an injection of horse serum produces supersensitiveness to horse serum alone, and not to sheep's or rabbit's serum. There is a period of incubation after the sensitizing injection during which a second injection produces no toxic effect. The existence of this preanaphylactic stage is a proof that the anaphylactic phenomenon is not due to cumulative action; it is shortest with an optimal dose of antigen. If the serum of an anaphylactic animal is injected into a normal individual, the latter soon becomes supersensitive—*i.e.*, it has been endowed with *passive anaphylaxis*, and reacts to an injection of the antigen with severe toxic symptoms (Otto). Similarly, the young of an anaphylactic mother exhibit supersensitiveness for some weeks after birth. The anaphylactic reacting bodies of the serum resist heating at 56° C. Now, it has been shown that the injection of foreign serum produces an immunity reaction with the development of precipitin. In general, the precipitin content of a serum and its capacity for conferring passive anaphylaxis run parallel (Scott and others). This is not always the case, however, and it has been found that the serum of a guinea-pig taken shortly after an injection of foreign protein conferred passive anaphylaxis on other animals either in large or small doses, but that later on only large doses of the serum were effective. Accordingly, Friedberger considers that the antiserum owes anaphylactizing capacity to the presence of the antiprotein immune body along with a trace of undecomposed protein antigen. But it is not clear how the latter acts. Supersensitiveness developed by injections of antigen persists for a long time (more than two years); passive anaphylaxis, on the other hand, disappears soon (after two to eight weeks). Observations on the behaviour of complement during anaphylactic shock have led to important results. The injection of antigen into a supersensitive animal produces, in addition to the symptoms already described, a great decrease in the serum complement. Proceeding from this observation, Friedberger treated complement (fresh guinea-pig's serum) *in vitro* with the precipitum obtained by mixing serum and the corresponding antiserum (sheep's serum plus antiserum from the rabbit), and found that the treated serum freed from precipitate by centrifugalizing produced all the phenomena of anaphylactic shock when injected into a normal animal. Accordingly, he concluded that a poisonous substance—*anaphylatoxin*—is produced when complement acts on the combination of antigen and antibody. Anaphylatoxin is also obtained when complement acts on bacilli treated with the corresponding immune body, even although no bacteriolysis results; this occurs in the peritoneal cavity as well as the test-tube. The quantitative conditions under which a fatal dose of anaphylatoxin is obtained *in vitro* are strictly comparable with those under which fatal anaphylactic shock is produced in an animal. The amount of bacteria—*e.g.*, *V. Metchnikovi*—required

to yield a fatal dose when treated with guinea-pig's serum, which contains a corresponding natural immune body, is much smaller (100 times) than the amount necessary to cause death from the action of the bacterial endotoxins. Optimal quantities of antigen, antibody, and complement, are necessary in order to produce a maximal yield of anaphylatoxin.

*Anti-anaphylaxis* is the term applied to the condition of insusceptibility (1) which can be produced by reinjection of the specific protein into an animal while in the incubation stage after a sensitizing dose, or (2) which immediately follows the injection of a sublethal dose into a supersensitive animal. The insusceptibility thus produced persists for some time, but subsequently disappears in the case of an actively anaphylactic animal; anaphylaxis which has been passively conferred does not return, however. Scott has shown that the specific antibody diminishes in the serum of an animal which has been rendered anti-anaphylactic—*i.e.*, a negative phase ensues. Friedberger holds that anti-anaphylaxis is due to the antibody being partially used up, so that a sufficiency does not remain over for the production of anaphylatoxin when antigen is subsequently injected. This explanation does not account fully for the peculiar conditions which enable the serum of an anti-anaphylactic animal to confer passive anaphylaxis. The cause of the anaphylactic phenomena appears to be a toxic action on the central nervous system, although Besredka's view that the intracranial injection of serum into a supersensitive animal produces effects in a smaller dose than an injection at any other site has not been generally accepted.

**Theories of Anaphylaxis.**—According to Richet, albumin contains congestin, which when injected into an animal leads to the formation of toxogenin. The congestin contained in the albumin of the second injection unites with the toxogenin, and leads to the setting free of apotoxin, which is a potent poison. Besredka holds that protein contains a body which he calls sensibilisinogen. This in the animal body leads to the formation of sensibilisin, which exists partly free in the serum, partly attached to cells. When the protein is reinjected, a second component, antisensibilisin, unites with the sensibilisin within the nerve cells, and thus gives rise to anaphylactic shock. The view that the reaction occurs within cells which contain sessile receptors has also been held by Otto and by Wassermann, but conclusive experimental proof of the action of sessile receptors is lacking. According to Gay and Southard, part of the injected protein, anaphylactin, persists in the treated animal, and acts as an irritant to the cells, so that they react abnormally with the protein injected on the second occasion. These theories are all somewhat incomplete. The view that anaphylaxis is due to an antibody reaction is held by Otto, Rosenau and Anderson, Nicolle, and by Friedberger. Friedberger considers, further, that the

reaction is merely a special form of the antigen-antibody reaction dependent on the peculiar quantitative relationships existing between the reacting substances, which results in the formation of highly toxic bodies. Anaphylatoxin consists, probably, of a mixture of peptone-like products resulting from a certain degree of protein breakdown. If the decomposition proceeds further—*e.g.*, if the mixture of antigen, antibody, and complement, is allowed to react for too long—non-toxic substances then result. Thus, anaphylatoxin formation depends on a specific antigen-antibody reaction, but the resulting toxic bodies are not peculiar to any given antigen. Friedberger's theory accords best with the majority of the facts. Primary antiserum action—*i.e.*, the immediate production of acute anaphylactic symptoms by the injection, *e.g.*, of anti-sheep serum from the rabbit into a guinea-pig—is thus explained by the presence of a suitable amount of the antigen which has persisted in the rabbit's serum. The immediate toxic action of an injection of the antiserum to an animal's own serum, or of a mixture of serum with the corresponding antiserum, is also easily understood on this theory. Toxic effects following immediately after a first injection of normal serum into an untreated animal would be explained by the presence of natural antibodies to the serum protein in the animal's blood.

**The Serum Disease in Man.**—When a first injection of foreign serum—*e.g.*, antidiphtheria serum from the horse—is administered, eight to ten days later certain symptoms occur in 10 per cent. of cases. These include fever, rashes, swelling of lymphatic glands, œdema, rheumatoid affections of smaller joints, and albuminuria. The results of a reinjection vary according to the interval intervening between it and the first injection: (1) if the interval is less than ten days, no further reaction takes place; (2) if the interval is twelve to forty days, an *immediate reaction* follows; painful œdema occurs at once at the site of injection, with general rashes and fever; (3) if the interval is over six months, an *accelerated reaction* occurs, the symptoms being the same as after the first injection, but they are more severe and of shorter duration, and occur after an abbreviated incubation period (four to six days); (4) when the interval is one and a half to six months, both the immediate and the accelerated reactions may occur. In animals there is, apparently, nothing comparable with the reaction following the first injection. The immediate reaction is, of course, analogous to the phenomena of anaphylaxis in the guinea-pig; but the occurrence of symptoms so severe as to cause death in the human subject is a very rare occurrence. Even more rare is the existence of such pronounced idiosyncrasy toward foreign serum that a first subcutaneous injection causes immediately severe or fatal effects. To avoid danger from a reinjection of serum, either a small dose should be injected preliminarily to the main reinjection (Besredka), or the serum

should be introduced very gradually (Friedberger and Mita), so as to produce a state of anti-anaphylaxis.*

*The Tuberculin Reaction.*—The supersensitiveness of tubercular subjects to tuberculin is manifested by the occurrence of symptoms after the administration of a dose which is without effect on a healthy subject. Thus, in cases of tubercular infection, tuberculin when injected subcutaneously produces fever (*tuberculin reaction of Koch*); injected into the skin it produces a local lesion (*Von Pirquet's reaction*); or when placed on the conjunctiva it causes conjunctivitis (*Calmette's reaction*). Certain observers have failed to confer passive supersensitiveness to tuberculin on normal animals by injecting the serum of tubercular animals which were themselves supersensitive, and have therefore sought to differentiate the tuberculin reaction from other anaphylactic phenomena; but the successful transference of supersensitiveness to tubercle bacilli (Friedberger and Mita) has removed this distinction.

Other pathological phenomena of the nature of anaphylaxis are—(1) Supersensitiveness to certain articles of diet—*e.g.*, of infants to cow's milk, and of some individuals to egg-albumin—which may pass off or may persist throughout life; similarly, urticaria, diarrhœa, vomiting, and asthma, which may follow the ingestion of strawberries, shell-fish, etc., in particular predisposed subjects appear to be anaphylactic phenomena: (2) idiosyncrasy toward certain drugs, such as iodides and antipyrin; these substances probably unite with certain tissue proteins and give rise to an antibody, as Friedberger and Ito have shown in the case of iodized albumin: (3) hay fever; this condition is apparently due to previous sensitization produced in susceptible subjects by inhaling the pollen of certain grasses, so that when subsequently the pollen again reaches the nasal mucous membrane and the conjunctiva anaphylactic symptoms follow.

**Anaphylaxis in the Infections.**—By graduating the amount of antigen which is injected into a supersensitive animal, it is possible to produce no other reaction beyond a disturbance of the temperature, which may be either depressed or elevated, according to the dosage employed. The occurrence of fever as an anaphylactic phenomenon suggests that febrile disturbance in many infective diseases may be of this nature, as sufficient quantities of bacterial protein are available in the tissues (Friedberger). It appears that the reaction to foreign protein in the animal organism may have either a detrimental or a beneficial result to itself, depending on conditions which are of a purely quantitative nature. In other words, the difference between supersensitiveness and immunity is

* Of course, danger of anaphylaxis is avoided if antitoxic sera derived from different species are employed—*e.g.*, a prophylactic dose of diphtheria antitoxin derived from cattle may be administered, and if later on the disease is acquired horse antitoxin can be safely given.

one of amount, and not of kind; but further investigation must show how far the balance of anaphylaxis and immunity explains the phenomena of infective processes.

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## CHAPTER VI

# DEGENERATION, NECROSIS, AND CALCIFICATION

By J. LORRAIN SMITH

Degeneration is roughly described as "intracellular" or "extracellular," and this division, while it is based on a fact of obvious importance, at the same time indicates one of the chief difficulties to be met in the attempt to form a general conception of the process.

If we consider the intracellular forms, such as the glycogenic, it is clear that we have to do with various kinds of abnormal metabolism, and in each case the particular variety is defined by the presence of a certain chemical constituent of the protoplasm, which may be of abnormal composition, or on the other hand may be normal substance present in unduly large amount. Many of the intracellular forms of degeneration remain undefined because of our lack of knowledge of the constituent concerned, and those which are better known are classified as fatty, glycogenic, mucoid, etc., according to the chemical character of the substance which accumulates.

As regards the extracellular degenerations, such as amyloid, the connection with cellular changes has not been clearly defined; and though it is easy to discover the presence of the amyloid deposits in the stroma, it is difficult to make out exactly where the disturbance has taken place which has led to the deposition. This difficulty, however, must remain till we have extended our knowledge of the normal relations of the cell to its surrounding stroma. Though widely different from active protoplasm, the stroma still remains in a very direct relationship to the vital integrity of the cells.

The present chapter includes, along with the description of the better-known forms of degeneration, a short account of necrosis and calcification. These changes are the usual termination of various forms of the degenerative process, and in the study of them we may obtain much information regarding the degenerations with which they are associated.

**Cloudy Swelling.**—That inflammation is accompanied by increased absorption of albuminous material by the protoplasm of the cell was put forward by Virchow as affording an explanation of the condition of cloudy swelling. The tissue which suffers from degeneration in this form appears opaque or turbid, and is slightly swollen. The condition occurs in the glandular organs generally, but especially in the kidney and liver; also in the heart muscle in infections and toxic disorders, and in the early stages of poisoning by phosphorus and arsenic. It is regarded by many pathologists, including Virchow, as due to an accumulation in granular form of albuminous material in the cell protoplasm, resulting from the inability of the cell to use up or integrate the material which it has absorbed. Again, it is observed that "cloudy swelling" passes gradually into fatty degeneration.

The kidney cortex is a most suitable tissue for the microscopic study of this condition in gland cells. Normal kidney cells show a protoplasm which to a large extent consists of minute granules, and to the swelling and irregularity of these granules is due the appearance of cloudy swelling. The normal granules were originally studied by Altmann in their relation to various functions of the cell, and especially in their relation to fat synthesis. Altmann applied Weigert's original myelin method, slightly modified, to the staining of these granules, and found that, like the medullary sheath of nerves, they stain readily with acid fuchsin after the tissue has been bichromated. From this there is a strong presumption that these granules contain some lipoid similar to that in the myelin sheath in its capacity of developing affinity for acid dyes when it has been mordanted by bichromate. That the granules at the same time have certain elements, albuminous in character, is concluded from the effect of acetic acid in clearing up the opacity of cloudy swelling. The granules of cloudy swelling are often observed as precursors of fatty degeneration. In other words, the granule is replaced as the process develops by a minute globule of fat, and, further, according to some observers, minute globules of fat are invariably seen in cells which show cloudy swelling. This consideration of the relation of cloudy swelling to fatty degeneration brings us to a further point of importance. The kidney which shows fatty degeneration is found on analysis still to contain only the normal amount of fat in its tissues; so that, whatever substance is added to the cell in cloudy swelling, it does not involve an addition of fatty matter.

Albrecht divided cloudy swelling into two forms: 1. Cloudy swelling without coagulation. This condition is well seen in the intact kidney when the other has been cut off from the circulation by ligature of its bloodvessels, or when the tissue has been flooded by an injection of sodium chloride solution. It is seen also in the kidney and liver in various infections, as in cases of pneumonia or empyema.

2. The second form is more severe in character, and in this case along with increase in granularity there is coagulation of the protoplasm. Evidence of this in the kidney is seen in the breaking away of fragments of the cells into the lumen of the tubules. With this there may be also a fine granular precipitation of albuminous particles. At the same time there is an increase of the watery contents of the cell, and an increased tendency to show in the protoplasm doubly refracting myelin particles.

Closely connected with cloudy swelling is the condition of hydropic degeneration, in which the accumulation of watery fluid leads to the formation of vacuoles in the protoplasm. This condition is well marked, for example, in the skin epithelium of smallpox vesicles.

Another form of degeneration frequently seen in the kidney, in the cells of the secreting tubules, leads to the formation in the cytoplasm of globules of hyaline refractile appearance, and markedly acidophil in staining. Whether this is to be classed with proteid-hyaline or acidophil-lipoid degeneration has not been determined.

It is clear that the interrelations of the granules, which appear in degenerative conditions of the protoplasm, to each other, and to the normal structure, must be the subject of much more investigation before we can reach a conception of their relation to those changes in metabolism from which degeneration results.

**Glycogenic Degeneration.**—Since the presence of glycogen in a tissue cannot be detected by the naked eye, the investigation of its occurrence can be carried out only by chemical or microscopical methods. To keep this substance in its natural form and condition in the tissue is also a matter requiring care, because, after the death of the cells in which it occurs, ferments are generated which change it into some form of sugar. Two such ferments have been recognized by Pick—one which is present in the blood and lymph, and changes glycogen into dextrose chiefly ; and another which is found in the salivary or the pancreatic secretion, and changes it into dextrin and dextrose. Ferments of this type are present in the various tissues, and their action, if unchecked, causes the disappearance of the glycogen. With this in view, the practice is to preserve the tissues in alcohol, and to regard only those which can be transferred to the alcohol without delay as affording reliable evidence on the occurrence of glycogen.

Muscle and liver both contain diastatic ferments, and some interesting observations have been made regarding differences in power of active fermentation in these tissues. Heart muscle, for example, has four to five times the power possessed by voluntary muscle ; and, again, the amount of fermentation shown by the liver varies at different times. The glycogen may disappear rapidly from the liver at one time, while at another several days may pass before it has completely disappeared.

Our information regarding glycogen is too scanty to permit us to reach any very clear conclusion regarding its occurrence in pathological conditions. As regards its origin in the body, the problem of its relation to proteins and fats and to other carbohydrates is still incompletely solved. It is of interest, however, to compare the conditions of its presence in pathological tissues with those which bring about the appearance of fat globules.

Glycogen occurs in the cell protoplasm of certain tissues of the body in the form of droplets and granules. It seems probable that it exists as granules in the living state of the cell, but, on the other hand, it is possible that—in some cases at least—the granular form of the deposit is due to the precipitation of the substance from solution in the protoplasm after the death of the cell.

It has been suggested by Lubarsch that glycogen assumes the granular form because it exists in the protoplasm in combination with the granules of Altmann, or some similar structure. In favour of this view is the regularity of the granular glycogenic deposit in certain tissues.

The glycogen of the liver is very soluble in water, but that found in squamous epithelium or in cartilage cells is relatively insoluble. From this fact Ehrlich draws the conclusion that glycogen exists in combined form in the tissues, but the substance to which it is bound varies in different localities.

Glycogen or some other carbohydrate is an essential constituent of all protoplasm. It has been found in all tissues except in the nervous system and in the mammary gland, but in both these tissues other simple or combined carbohydrates occur in characteristic form.

Since glycogen, like fat, occurs in physiological conditions so commonly, it is only when it shows some direct association with pathological conditions that we can regard its presence as indicating degeneration.

1. It occurs in the protoplasm of leucocytes which appear in inflammatory foci during the earlier stages of pneumonia, and in those of abscesses and other sources of suppuration. It is found in the leucocytes of phthisical sputum, but it is absent as a rule from those which are found in tuberculous foci of long standing and in syphilitic gummata. It is present in the cells of a recent tuberculous focus set up by experimental injection.

2. It is found in the looped tubule of Henle, a tubular segment in which globules of fat are commonly deposited. According to Gierke, fat droplets are to be seen in these cells, along with the granules of glycogen, in experimental diabetes.

3. Excessive amounts of glycogen are often found in the tissue of neoplasms. Lubarsch examined 1,544 tumours, and found it present in 447 cases, or 29 per cent., in quantities to be detected by microchemical methods. It is practically absent from all innocent

tumours. On the other hand, as compared with that found in the normal tissue, it is increased in amount in enchondroma and rhabdomyoma. It is abundant in periosteal sarcoma, and it is almost invariably present in hypernephroma, and sometimes in enormous quantity. It is found also in endothelioma cells, though it is absent from normal endothelium. Speaking generally, it occurs in tumours in young subjects, though it is not confined to these, nor does it necessarily accompany great energy of growth. It has been observed, further, that when the primary tumour is rich in glycogen, the metastatic growths have the same characteristic; but this quality is lost if the progress of the tumour lead to a marked development of cachexia.

It is evident that we are as yet without the data for a clear definition of the process of "glycogenic degeneration." Since glycogen is so easily changed into other forms of carbohydrate, and since its combined forms are so little understood, we are unable to deal with it in the same way as with fat. Fat is much more stable in the tissues. We have arrived by chemical analyses at an estimate of fat as a normal constituent of the various tissues, and we can therefore measure its increase in pathological conditions. In the study of glycogen we find many points at which it shows in its occurrence a resemblance to fat, but we must wait for further investigation before we are able to understand its association with pathological conditions. The conceptions of fatty degeneration which are now adopted depend chiefly on quantitative analyses, and the difficulty in regard to glycogen is mainly due to the fact that similar methods of analysis cannot as yet be applied in its case. Its occurrence has been studied by various histological methods depending on the iodine reaction, and also on certain staining processes. The iodine reaction consists in a dark brown staining of the glycogen granules or droplets with weak solutions of iodine in iodide of potassium. Confusion as regards the differentiation between amyloid and glycogen is easily avoided by contrasting the sites of the deposit. Glycogen is intracellular, while amyloid is found in the fibrous matrix. Amyloid shows a contrast to glycogen in the fact that it is much more insoluble in water, and it resists salivary digestion, while glycogen fails to give the iodine sulphuric acid reaction and the pink colour with methyl violet which are characteristic of amyloid substance.

For the purpose of histological study of glycogen, Ehrlich recommends a medium prepared by the addition of Lugol's solution (iodine 1, iodide of potassium 2, water 100), 1 part to 100 thick gum. In this medium preparations may be mounted; but though it is valuable for the study of films, preparations of blood and pus, it is not sufficiently transparent for use in the study of sections.

Barfurth recommends the use of a mixture of Lugol's solution,

1 part, with glycerine, 2 parts. This medium, while clearer than Ehrlich's, loses the iodine more quickly.

Another iodine method was introduced by Langhans. The sections, after being submitted to the action of Lugol's solution for ten minutes, are washed in a mixture of tincture of iodine and absolute alcohol, and then transferred to origanum-oil, in which they can be preserved. When the iodine has evaporated, the brown colour can be restored by again submitting the section to Lugol's solution.

As regards staining methods, the tissue which is to be sectioned should be hardened in alcohol. While certain of the less soluble forms of glycogen can be studied in formalin or sublimate-fixed material, the study of pathological deposits should always be carried out in material fixed in alcohol. Lubarsch has introduced a method of staining the glycogen granules by gentian violet in anilin-water (one to two minutes), fixation of the stain by Gram's iodine solution (five to ten seconds), and dehydration and differentiation by anilin-oil xylol. This preparation shows granules stained a deep blue, and may be mounted as a permanent preparation in Canada balsam. The nuclei of the cells may be coloured red by Mayer's alcoholic carmine. While this method is not universally applicable, it rarely fails to stain substances which give with iodine the characteristic reaction of glycogen.

Lubarsch also recommends the use of a stain formed by a mixture of Gram's iodine solution and hæmatoxylin, which gives a contrast between the blue nuclear staining and the brown colour of the granules of glycogen.

The other staining method is that introduced by Best, according to which carmine is used in ammoniacal solution after careful preparation. The stain is applied for an hour, and then differentiated by ammoniacal alcohol. This method is particularly successful with tissues which have been sectioned in celloidin.

**Fatty Degeneration.**—Fatty degeneration is perhaps the most frequently observed among pathological changes. It results in the formation in the cell protoplasm of globules of fat. Degeneration is to be contrasted with physiological infiltration, however, in that it is associated with some morbid condition of the tissue, and the accumulation of visible fat in the cells takes place in the absence of any excessive supply of it in the diet. That the accumulation of fat is the result of degeneration may be recognized by the microscope, especially in the cases where the breakdown of the cell as a whole has occurred at the same time.

The frequency with which this degeneration is observed may be explained in two ways. It is, in the first place, a change which occurs in practically all the tissues of the body, and, on the other hand, it is an important part of the morbid processes of the great majority of diseases. It is seen in conditions so widely different

as those of acute toxic diseases on the one hand, and in chronic anæmia on the other.

It is, further, important to note that the experimental study of the degeneration is easy of accomplishment, since the condition can be produced with certainty in animals by the administration of poisons such as phosphorus and chloroform. As a result of this our knowledge of the process has been greatly extended.

To these considerations there is to be added the fact that there are abundant histological and chemical methods available for the study of the affected tissues.

In virtue of these general facts, fatty degeneration has been the subject of study beyond any other type of morbid metabolism, and the conclusions arrived at have been of fundamental importance in the study of degeneration in all its forms.

The fatty substances of the body are either fats or fat-like bodies called "lipoids." The fats in the tissues are usually neutral fats, which are glycerinesters, composed of glycerine and fatty acid, and of these there is a large series, but those most frequently met with are olein, palmitin, and stearin.

These fats are deposited most plentifully in adipose tissue, which is found distributed through the body generally, in situations where connective tissue is abundant. Its peculiar character is due to the power which the cells possess of forming a store from which fat is transported when the active tissues of the body require it.

The fat cell in its earliest form has the granular protoplasm and central nucleus of the typical connective-tissue cell. In the protoplasm there appear fine globules of fat formed round the granules. These globules gradually enlarge, and when they have reached a certain size the separate globules coalesce to form one, and this becomes finally large enough to occupy the whole cell. The nucleus at this stage is pushed to one side, and the protoplasm forms little more than a capsule for the globule of fat. It is observed that the growth in size of the large single globule takes place because the protoplasm continues to form fine globules, which on reaching certain dimensions pass to the large globule and add themselves to its bulk. In the adipose tissue of the young embryo the fat does not always form a single large globule, but remains as several distinct globules occupying the protoplasm. When there is a demand for fat by the active tissues of the body, this store material is given up, and transported by the blood to the site where it is needed.

We have yet much to learn regarding the method of transport and the mechanism by which it is regulated. The fat may be carried away in the form of minute droplets, as a soluble soap, or in some other combination. It has been found that in the adipose tissue in a case of starvation the fat cells frequently show one large and several smaller globules. In the lipæmia which is observed in

cases of diabetes we have an example of disorganized transport. The plasma of the blood contains an excessive number of fat droplets, and accompanying this there is a general occurrence of fatty degeneration in the glandular organs. The analyses of the fats and lipoids found in the blood in this condition show an excess of cholesterin, and indicate that, as regards both the quality and the quantity of the fatty material, the transport is abnormal.

Fat is stored in normal tissues other than adipose tissue, and the liver in particular among glandular organs shows globules of fat in the epithelial cells in physiological conditions. Fat which is stored in this way in visible globules is described as infiltration fat. To carry this reserve material is part of the normal function of these structures, and the cells show no sign of injury. When the globule is used up, the space which it occupied is no longer to be seen, and the cell remains intact. Here, as in the case of the adipose tissue, the cell's power of accumulating a large mass of fat is associated with minute granules in the protoplasm round which the fat gathers. We may in this respect compare the process to one of secretion. The composition of the minute granules and their relation to fat is not yet understood. According to a number of investigators, the granules are lipoid in nature, but the application of microchemical methods has not yet made clear the exact nature of the lipoid substance. It is obvious, however, from the facts which have already been brought forward, that the cell deals with fat by means of a complex mechanism which we recognize and stain in the form of granules.

The group of substances which we have classified as lipoids is, as compared with the fats, much less clearly defined. It includes substances widely differing from each other in their constitution, but they have in common the property of being soluble in fat solvents. They are universally distributed through the body, in the tissues, and in the blood, generally in small amounts. They are abundant, however, in the tissues of the nervous system, and especially in the myelin of the white matter. Myelin, though composed of a number of lipoid substances, has at the same time certain characteristics. It is doubly refractile to polarized light, and is therefore in a fluid crystalline condition. When a mass of it is brought into contact with water, it forms doubly refracting globules, or sends out from its surface into the water finger-like projections, which are known as "myelin figures." This curious property probably depends on the surface tension which is established in the presence of water. The production of myelin figures is a characteristic power not only of the complex myelin itself, but also of some of its component substances, such as the cerebrosides.

Further, it stains with osmic acid, but does not stain in Marchi's fluid. From this we may gather that it contains unsaturated bodies which are easily oxidized.

We know very little indeed regarding the deposition of myelin in nerve tissue, but by the use of thionin blue and other basic dyes the presence of a network in the myelin sheath can be demonstrated. This suggests an origin in protoplasm in separate masses similar to the granular origin of fat, but on this point observations are still wanting.

Myelin is found also in the cortical cells of the normal suprarenal body. Under the action of formalin fixation this myelin assumes the solid crystalline form. It passes into the fluid crystalline phase again, however, if it be heated in glycerine or gum.

The classification of lipoids which is generally adopted has been set forth by Rosenheim as follows: (1) The cholesterin group, the members of which are free from both nitrogen and phosphorus; (2) the cerebro-galactoside group, the members of which contain nitrogen, but not phosphorus; (3) the phosphatide group, which contains both nitrogen and phosphorus. Members of each of the three groups of lipoids are found to be essential elements in the white sheaths of nerves or in the myelin of the suprarenal. How far they enter into the myelin or myelin-like substances which are obtained from the other tissues of the body has not been fully determined.

Recently the study of fatty degeneration has shown the frequent presence in pathological tissues of deposits of lipoids, which, if not of the same composition as myelin in the nervous system, still have the characteristic physical properties. These products of degeneration are found in a large variety of situations, such as atheromatous patches in the intima of bloodvessels, tubular epithelial cells of kidney, the lymphatics, and the alveolar cells of the lung, tumours, cysts, etc. Here they occur as doubly refracting solid or fluid crystals in the tissues, giving myelin figures when brought into contact with water. Some authors have classified degenerations, in which this type of substance appears conspicuously, as a separate group, but it is doubtful if this step is justified. Since the importance of these substances in general pathology has come to be recognized, the question naturally arises how far they are concerned in the ordinary form of fat metabolism on the one hand, and of fatty degeneration on the other, and only the answer to this question would enable us to settle the classification in a satisfactory way.

So far we have discussed fat and lipoid substances as they may be seen when the tissue is examined by the naked eye or microscope. There remains, however, another form of fat—that which is called "masked fat." If we take a tissue such as heart muscle, which contains little or nothing in the form of visible globules of fat, and, after drying it, extract it with boiling chloroform, we obtain about 15 per cent. of the dried tissue dissolved out in the solvent. Such fat is not detected by ordinary histological methods, and to obtain the complete yield of material a prolonged extraction is required.

It is possible that at the temperature of boiling chloroform decomposition of the molecules containing fat or lipoid substances takes place, and that the solvent while extracting is also splitting off the fat or lipoid from the bodies with which they are combined. There is, however, no doubt a great difficulty in dissolving some of the substances which are obtained during the later stages of the extraction, and in the meantime it is impossible to define chemically the nature of "masking." The difficulty of extraction is sometimes overcome by digesting the tissue in pepsin and hydrochloric acid, or by breaking it up by means of soda or potash, which form soaps by combining with the fatty acids. The heart muscle so treated will yield about 15 per cent. of the dried substance to fat solvents, and the kidney similarly extracted will yield about 18 per cent. We shall see later the importance of this form of fat in the discussion of the nature of fatty degeneration. It is the fat which, being intimately combined with the protoplasm, is directly concerned in metabolic changes, while the fat which is visible as globules is in a sense separated from the protoplasm in which it is situated.

The methods by which fatty degeneration has been studied are histological or chemical, and a point of special interest in regard to them is the development of combined methods which are at the same time chemical and histological.

*Histological Methods.*—The first method which gave differential staining of fat was the osmic acid method. The peroxide of osmium forms a colourless solution in water, and this, when it acts on fat in tissues, gives a black stain which is very sharp and characteristic. Altmann was the first to show that this reaction, chemically speaking, is the oxidation of the unsaturated fats. In contact with olein, for example, the peroxide of osmium is reduced, and it forms with the molecule which it is oxidizing a black compound, which is insoluble in xylol and other solvents. Osmic acid therefore is a fixative agent as well as a stain, and if the globules of fat be sufficiently fixed as well as clearly stained the section containing them can be mounted as a permanent preparation in Canada balsam. Osmic acid stains fat readily in adipose tissue in the liver, in degenerating heart muscle, in the kidney, etc., since these deposits all contain olein. It also stains the normal as well as the degenerated nerve fibres of the brain and spinal cord, if the tissue has been preserved in formalin or other non-oxidizing fluids.

The next method to be described is that of Marchi, in which the principle of selective oxidation is introduced. Marchi in the first place applies bichromate of potassium to the tissues, so that it may oxidize the easily-oxidized substances of a fatty nature, while those which are more difficult to oxidize are left to a large extent unchanged. If osmic acid be then applied, it stains fatty substances which, though oxidizable, have yet escaped the action of

the bichromate, and these it colours black. This method finds its most striking application in the study of the degeneration of nerve fibres in the central nervous system. The normal myelin of the medullary sheath oxidizes very readily under the action of the bichromate, whereas the degenerated myelin oxidizes very slowly. The bichromate does not give any distinctive colour to the myelin which it oxidizes. By its rapid action on the normal fibres it becomes practically selective, and leaves only the degenerating fibres to receive the black stain. That the method is of fundamental importance in neurology needs no further explanation.

By the same principle it has been shown that on the oxidizing action of bichromate the staining of fat by hæmatoxylin depends. The action of bichromate on olein, for example, occurs in stages. At one stage of the process a compound forms, in which one molecule of $CrO_3$ attaches itself to a molecule of oleic acid. This forms with hæmatoxylin an insoluble blue lake. At a later stage in the process, this chromium compound is so altered by the further continuance of oxidation that it shows no affinity for the hæmatoxylin. For staining purposes it is overchromed. In other words, Weigert's stain for the medullary sheath is a universal stain for unsaturated fats and lipoids. Fat, as it appears in the liver, or in adipose tissue, is composed chiefly of olein, and, as it is an unsaturated body, it is slowly oxidized if exposed to bichromate solution. To apply the method to the study of fatty liver, etc., it is of advantage to cut the tissue in frozen sections after rapid fixation in formalin, and expose the sections to bichromate in saturated solution at 37° C. In a fortnight or so the globules of fat in the section will show excellent results if stained with Kulschitzky's acid hæmatoxylin, and differentiated by the borax and ferricyanide of potassium solution, which Weigert used for the myelin method. Similarly, Pal's, or any other modification of Weigert's original method, may be used. The same result can be obtained by the ordinary bichromate fixative, which is used at ordinary room temperatures, and which contains about 2 per cent. of the salt, but it takes an exceedingly long time to carry the fixation to the required point.

Here, again, as in the use of the Marchi method, we may study the rate of oxidation by observing the time required to obtain the staining reaction, and results of much interest are obtained in comparing in this respect the lipoids in various tissues.

Another group of methods of great importance is that in which use is made of the anilin dyes, and they illustrate the following principles:

1. Certain of the anilin dyes are very soluble in fat, and they impart to the globules in sections a brilliant colour. Of these, Scharlach R and Sudan III are the most familiar examples. They belong to the azo group of dyes, and are chemically indifferent bodies.

2. The chemical affinity of the dye may be made use of, and we have accordingly basic and acid stains. Any basic dye will stain acid fat, and it forms a soap-like compound which has the colour of the dye. To apply these stains, therefore, we have to hydrolyse the neutral fat, and split it into its component glycerine and fatty acid; and this can be done by the action of dilute acids, or even by the action of the carbonic acid of the air if the section be exposed to it for some time in a layer of glycerine or gum. It is often to be noticed that, in staining sections of liver for amyloid disease, the methyl violet which colours the amyloid pink, at the same time colours the globules of fat violet. The fat is acid, and combines with the base of the dye, but the acidity of the fat in tissues which have been preserved in formalin may be due to the hydrolysis which is set up by the acid formed in the formalin.

In contrast to this we have staining of myelin with acid dyes such as acid fuchsin. It is interesting to remember that this dye was the first which Weigert used in staining the nerve sheath. The rationale of this method is suggested by a study of cerebroside, the components of which are, as Thierfelder has shown, a reducing sugar, a fatty acid, and a basic lipoid substance, to which the name "sphingosin" has been given. This substance exposed to acid fuchsin in watery solution takes the dye readily.

3. Finally, in one group of dyes, the oxazines, of which Nile blue sulphate A is a member, we find substances which in watery solution act as double stains. The one stain is an example of basic staining by the oxazine base, which forms a blue compound with fatty acid, and in this Nile blue sulphate resembles other basic dyes. The second is due to the fact that the oxazine base decomposes in watery solution, and forms oxazone, which is a body resembling Sudan III in being chemically indifferent and in being soluble in liquid fat. At the same time it has a brilliant red colour. The result is that the globules which contain acid fat are stained blue, while those that consist of neutral fat only are stained red. In using this dye, care must be taken to avoid the effect of fixatives on the fat in the tissues. Formalin solution, for example, becomes sufficiently acid to bring about hydrolysis of the fat if the tissues are kept in it for some time.

It is obvious that the staining of a given globule of fat with any of the dyes mentioned does not prove that it is fat in the strict sense of the term. We may conclude, however, that a substance staining in the way described is either fat or lipoid, that it is neutral or acid, and that it is saturated or unsaturated.

*Chemical Methods.*—The chemical investigation of fats and lipoids is carried out by the ordinary methods of analysis, and we need not, in describing this part of the subject, give details which find their place in a practical textbook. It will be sufficient to indicate

the principles of such methods as have been found specially applicable to the problems which the subject presents.

The tissue may be dried at a temperature not above 37° C., so that decomposition may be avoided, and the dried tissue is then extracted by various solvents. Chloroform, ether, acetone, and alcohol, are those most commonly used. The extraction may be carried out in a Soxhlet apparatus, but a more effective method is that of suspending the thimble in the boiling vapour of the solvent under a reflux condenser. The total extract having been obtained, the various substances may be separated by taking advantage of their relative solubilities. Cholesterin, for example, is readily soluble in cold acetone; lecithin and cerebroside, on the other hand, are relatively insoluble. Cholesterin is readily isolated by precipitation with digitonin by Windaus's method.

In order further to separate the bodies, methods of saponification with caustic potash in alcohol or by sodium ethylate are adopted. The sodium or potassium soaps are soluble in water, and they can therefore be separated from the unsaponifiable substances, such as cholesterin, which are insoluble in water. Further, as we have already seen, the saponification of the fat by strong alkalies has been used for the purpose of extracting masked fat from dried tissue.

The use of barium hydrate dissolved in methyl alcohol has been introduced for the purpose of saponification. Barium soaps and other barium lipoid compounds are highly insoluble, and therefore, as the saponification takes place, the soap is precipitated. Apparently for a similar reason, cerebroside is precipitated also from the boiling methyl alcohol solution of baryta; and as it can be extracted from the dried precipitate with boiling acetone, in which barium soaps are insoluble, this forms a very easy way of isolating cerebroside along with the unsaponifiable substances.

Another method of investigating the lipoids is to estimate their decomposition products. Lecithin, for example, has been investigated by estimating the phosphorus. Cerebroside has been estimated by observing the amount of the reducing sugar which is obtained from it by hydrolysis with mineral acid.

Again, the unsaturated fats and lipoids are studied by estimating the absorption of oxygen from permanganate of potash, or the absorption of bromine or iodine. By this means there is obtained an absorption index which expresses the proportion of unsaturated molecules present among the fatty substances.

Since many of the fats and lipoids are crystalline at ordinary temperatures, and not a few have a fluid crystalline phase, it is important to study the clearing-point by a polarizing microscope fitted with a hot stage. By this means the exact temperature of the clearing-point can be ascertained, and in the case of degenerating myelin this method gives in the lowered temperature of the clearing-

point a definite indication of the presence of degeneration. The sections are cut with the freezing microtome, and mounted in glycerine. They are then examined on a hot stage which gives temperatures up to over 200° C. This high temperature is required for the testing of cerebrosides.

**The Occurrence of Fatty Degeneration.**—We have already pointed out that fatty degeneration occurs in all the tissues of the body. The secreting glands, the muscles, the nerve fibres, the bloodvessels, the lymphatics, the connective tissues, and even the quiescent cells of cartilage, show the accumulation of globules of fat or lipoid in pathological conditions. The causes of this change are also very numerous, and we may classify them in groups :

1. Among the most important causes of this condition are the bacterial toxins, and hence we meet with this change in acute infectious diseases, such as diphtheria, pneumonia, pleurisy, and pericarditis. The heart, liver, and kidney, frequently show degeneration in these conditions.

2. The endogenous poisons in such conditions as jaundice, diabetes, eclampsia, cause degeneration in the liver and kidney.

3. A large group of poisons, of which phosphorus is the best known, but which includes arsenic, chloroform, iodoform, carbolic acid, causes degeneration.

4. Anæmia in general, but especially pernicious anæmia, causes degeneration, particularly in the muscle of the heart.

5. Atrophy of various forms is a frequent cause—for instance, the atrophy of old age, that accompanying chronic venous congestion, atrophy from disuse.

6. In certain forms of disease, fatty degeneration is a conspicuous change. An example of this is seen in the kidney in the parenchymatous form of Bright's disease, in the subacute stage. The size and pallor of the organ leads to its name of "large white kidney," and the colour is in great measure due to the presence of fat in the epithelium. Acute and subacute yellow atrophy of the liver also occasion fatty degeneration. Here the degeneration is often of the most advanced type, and with it disintegration of the cell structure is seen, frequently almost complete in the case of the liver, and to a less extent in the kidney.

7. Fatty degeneration is often observed to accompany amyloid degeneration. While the connective tissue of the liver and kidney is loaded with amyloid substance, the epithelial cells often show fatty change.

8. The spontaneous disintegration of nerve tissue which has been deprived of its blood-supply, or otherwise injured, is called "fatty degeneration." The myelin collects in drops, which stain by Marchi's method, because the complex lipoids of the myelin are decomposed.

9. We know very little regarding the transportation and circulation of fat and lipoids, but in view of its importance a special note is called for in regard to the form of degeneration observed in the walls of bloodvessels and lymphatics. On the surface of the aorta of even young individuals, yellow streaks are often noticed, indicating the deposition of fat and lipoid in the intima. The star-shaped cells of the intima undergo a form of fatty degeneration, and the deposit is partly fat; but there is also a lipoid substance, which in formalin preservation assumes the form of definite irregularly needle-shaped crystals, but which in the fresh condition is in a fluid crystalline form. This substance is deposited in the cells in isolated masses, and when the tissue is treated by the paraffin method, and sectioned, the whole of the lipoid material is dissolved away, and the cell then presents a reticulated protoplasm, sponge-like in appearance, from the multitude of small spaces which then appear as vacuoles. In this case, possibly from the nature of the substance, coalescence has not taken place, and a large globule has not formed in the way which is so characteristic of cells in which the material consists chiefly of liquid fat. These cells are sometimes called "foamy cells." The deposition of the lipoid substance in the intima is not diffused, but occurs in patches or streaks. So far, however, nothing has been discovered which explains their formation. Some cases show a deposit in lines which form a complicated network in the intima, occupying especially the part of the aorta which surrounds the openings of the intercostal arteries.

The very definite lines in which it is found are suggestive of lymph spaces, yet the attempt to discover in the intima of the aorta definite lymph channels has not so far succeeded. The importance of this form of degeneration, however, lies in its relation to that which occurs in the intima in atheromatous arterio-sclerosis. In the patches of thickening which are found in this disease, there is very commonly, if not invariably, a focus in the form of an area in which fat and lipoid substance are deposited in cells of the same form as those we have just described in the simpler case of fatty degeneration of the intima. Here a further development is to be noted. The cells which contain the lipoid deposit easily and readily undergo necrosis, and the area breaks down, forming a softened centre in the atheromatous patch. The origin of the lipoid substance in these areas is still a problem. Jores holds that the degeneration is an essential part in the process of arterio-sclerosis, and therein opposes the older view of Virchow, who regarded the fatty degeneration as a secondary change in patches of fibrous thickening.

As regards lymphatic channels, the deposit is to be observed in various situations. When the lacteals of the intestine are blocked by tumour growth, we may find an accumulation of crystalline fat in the lumen, while the lining cells are loaded with myelin globules;

and when these are cleared away by solvents, the cells have the reticulated structure already described. Another important point to be made out here is that with this there is in the walls of these lymphatics an overgrowth of the endothelial cells. They multiply in number, and some of them also show a large number of nuclei. This is still more clearly seen in the walls of simple cysts of the mesentery in which the contents are of a fatty nature. Again, the same type of cell is seen in the lumen of intestinal lymphatics which are the seat of tuberculosis, and it is to their presence, as well as to the caseation, that the characteristic yellow appearance of these lymphatics is due.

In a recent paper, Stheeman (*Ziegler's Beiträge*, 1910) has argued that the lymph-glands are concerned in fat metabolism, in the sense that fat passing from the reserves to reach the circulation is carried by the lymph-stream, and in the glands it is absorbed by the microphages and modified in a manner which he compares to an internal digestion. He also concludes, from an examination of fœtal tissues, that the walls of the lymphatics in these early tissues have some of the power of modifying fat which in the adult is restricted to the lymph-glands. His results are of interest because they point to the importance of the changes which the fat and lipoids may undergo in the course of the lymph-stream.

10. Apart from definite lymphatic vessels, myelin deposits in endothelial or connective-tissue cells are occasionally met with here and there throughout the body—in areas of inflammation, in the matrix of tumours, in the fibrous bands of cirrhosis, and elsewhere.

11. A form of fatty liver is observed in cases of tuberculosis, and especially in phthisis pulmonalis. It has been generally believed that here the fat is due to infiltration, and in the less advanced cases the deposit occurs only in the peripheral zone of the acinus. As the condition becomes more marked, however, it spreads to the centre of the lobule, and gradually involves the whole of it. The reasons given for regarding this condition as an infiltration are that it is, in the first instance at least, confined to the outer zone, and also because the fat appears in large globules. Degeneration, on the other hand, is characterized by small globules diffused through the protoplasm. and not confined to one zone of the lobule. We shall refer later to this contrast, but in the meantime certain points claim consideration. Though when degeneration begins, there are small globules, yet as it becomes advanced it shows large globules, and when this stage has been reached it would be difficult to apply the distinction between degeneration and infiltration in the liver from a mere study of the appearances of the tissue. At the same time, we have already explained that infiltration, as it is most typically seen in adipose tissue cells, begins in small globules, and the large globule grows by the formation of new small globules round protoplasmic granules. In the next place, the localization

of the deposit to the peripheral zone, as has been already pointed out, is seen only at the beginning of the process.

When the liver of cases of tuberculosis is examined microscopically, it will be found that very frequently miliary tubercles are present in the connective tissue of the portal area, and as a rule it is that part of the peripheral zone of the acinus which abuts on the tuberculous focus that especially shows the presence of fat globules. The remaining part is free, so that the deposit of fat is discontinuous in the peripheral zone of the acinus. This type of fatty liver, which has been called the "granular fatty liver," seems to be due to a direct effect of toxin arising in the focus of tubercle. In other words, this fatty change is degenerative in origin.

Enough has been said in the meantime to show that the fatty liver of tuberculosis is not a simple example of excessive infiltration in an organ otherwise normal.

The same conclusion seems justified in the case of the "simple fatty liver" due to alcoholism.

In this connection reference must be made to a form of fatty infiltration where the tendency to accumulate fat is shown by the connective tissue. This condition is observed in the stroma of the pancreas, where it is called "lipomatosis." It is also very commonly seen in the subepicardial tissue, especially that of the right ventricle. While it is strictly subepicardial to begin with, it extends later between the muscle fibres, and causes them to atrophy, degenerate, and disappear. It is this condition which is described in the English textbooks as "fatty infiltration." Occasionally also in the patches of fibrous tissue which are found in the muscle in myocarditis, a few of the cells may assume this adipose form. The clinical conditions associated with this change are not in general well defined.

**The Origin of Fat.**—The origin of fat in the body has been a problem of much interest in physiology, and it has direct bearing on the subject of fatty degeneration. The view that Virchow put forward regarding fatty degeneration was that fat arose from the disintegration of living matter, the fat being a part of the wreckage. At the same time it was held that living matter was practically protein, and that other elements in the protoplasm were adjuncts. Fatty degeneration being the breaking down of the living matter, it was too readily assumed that the fat was derived from protein. That the living matter of the animal body is able to transform carbohydrate substances into fat has been clearly proved by estimating the increase of fat in an animal on a carbohydrate diet, but no evidence that is beyond criticism has been offered as yet to show that fat may arise from a transformation of protein by the animal tissue. Voit, who brought forward this doctrine as a positive conclusion, found in Pflüger a critic who has left the question still unanswered. Voit observed that dogs, when fed on a diet of lean

flesh, retain a certain amount of the carbon, though they eliminate the whole of the nitrogen of the food. To explain this, it was pointed out that the retained carbon is partly utilized to form glycogen, but this would not account for the whole of it. Since Voit published this conclusion, various facts have been discovered which make the conclusion doubtful. The calculation of the ratio of nitrogen and carbon in lean meat was not sufficiently accurate, and the correction of this, which the later investigation of Rübner supplied, showed that the retention of carbon had been much exaggerated by Voit. Again, it has been found that in normal muscle a considerable amount of the carbon is in the form of fat or carbohydrate already. Rosenfeld has proved that muscular tissue, which to the microscope may be devoid of fat, still contains in it a quantity amounting to 15 per cent. of its dried substance. Pflüger has shown that muscle contains a similar quantity of glycogen. The fattening effect of a diet of lean meat might be explained, therefore, without involving the transformation of protein into fat. On the other hand, there are grounds for believing that protein gives rise to glycogen, and it may be that indirectly protein is a source of fat in the animal body. We may conclude, therefore, that the fat appearing in a cell in the process of degeneration may arise directly from the protoplasm of which it forms an essential element, or indirectly by the transformation of some other constituent of the protoplasm, lipoid, carbohydrate, or even possibly protein.

**Experimental Study of Fatty Degeneration.**—Apart from the investigation of the transformation of other substances into fat, there has been a considerable amount of experimental evidence brought forward on the transport of the fat which appears in degenerated tissues. The investigation has been made by introducing into animals fat of a known composition in order to study its deposition and transportation. This has been rendered possible because the fat of one animal differs in composition from that of another, and at the same time, if an animal—for example, a dog—is fed with the fat of another species (sheep), the mutton fat is deposited in the storage tissues of the dog, and can then be identified by its iodine index and other characteristics.

Lebedeff, Rosenfeld, and others, have carried out experiments by this method. A dog was starved till its depot fat was exhausted, and it was then fed with mutton fat, and with this its storage tissues became filled. It was next subjected to phosphorus-poisoning, and the fat in the degenerated heart muscle which resulted was shown to have the iodine index of mutton fat, and not of dog fat, as might have been expected had the fat in the myocardium resulted from the breaking down of dog tissue by the phosphorus. This result is obtained also when the experiment is carried out with phlorhizine, which causes fatty degeneration of the liver.

Another method which arrives at the same result was suggested by the observation of the effect of phosphorus on a man in a state of extreme emaciation. Lebedeff relates a case of this kind in which the phosphorus produced no fatty degeneration of the liver. A similar result has been obtained experimentally in dogs and fowls. Some very recent investigations point to the conclusion that phosphorus in starvation does bring about the separation in the cells of globules of myelin which stain with osmic acid, but not with Scharlach R.

As a result of this series of investigations, certain authors have included in their definition of fatty degeneration the accumulation of fat transported from storage tissues; but before considering this mode of regarding degeneration we must refer to another series of experiments.

Dudgeon and Leathes, experimenting with guinea-pigs, injected diphtheria toxin in such quantity as to cause fatty degeneration of the myocardium to a marked degree. They then compared the extracts of the degenerated and the normal myocardium, and found that the increase in fat was very slight in amount. The higher fatty acids formed 2·05 per cent. of the normal myocardium, and 2·23 per cent. of the myocardium in those on which the toxin had acted. It is difficult, as Leathes remarks, to believe that the addition of fat, to the amount of 0·2 per cent. of the tissue, would explain the striking difference in appearance between the normal and the poisoned heart.

The comparison of the normal and degenerated kidney in phosphorus poisoning has in the same way shown that not only is there no increase, but that in the so-called "fatty kidney" the fat present may be less (16 per cent. of the dried substance) than that which is masked in the normal kidney (18 per cent. of the dried substance). In such a case, then, we must regard the degeneration as the unmasking of the content of fat normally held by the protoplasm. The same results have been obtained in comparing the analyses of the normal liver in the cat with those of the organ which has been reduced to a state of fatty degeneration by ligature of the hepatic artery. In this case there is no increase of fat in the degenerated as compared with the normal tissue. It has been pointed out that in the case of the liver, when poisoning by phosphorus takes place in ordinary conditions of nutrition, fat accumulates in the liver cells in large amounts. Experiments have shown that fat is transported there in these conditions, whereas, as we have pointed out, it is possible to induce the condition of simple degeneration, without increase of the fat in the liver, by ligature of the hepatic artery.

The conclusion from these experiments is that, in those tissues in which storage of fat does not normally occur, degeneration from phosphorus poisoning occurs with little (heart muscle) or no (kidney) increase of fat in the tissue; but, on the other hand, in the

storage tissue of liver there is definite increase in the amount of fat, which can be explained only by transportation.

**The Nature of Fatty Degeneration.**—The account of the various investigations which have been already described gives us the means of obtaining some conception of the process involved in fatty degeneration. The exact form in which fat is an essential constituent of protoplasm is difficult to determine, but it is sufficient for our present purpose to point out that it normally enters into the living structure in a certain proportion according to the type of tissue examined. In the protoplasm it disappears from the view of the microscope, and cannot there be identified clearly by any staining method as yet known. In this condition it is said to be masked. It can be obtained from the dried tissues by means of fat solvents, so that the combination which takes place between the fat and other constituents of the protoplasm, while it is sufficient to conceal it from histological search, does not take the form of a compound which fat solvents fail to break up. On the other hand, the fat of infiltration appears as globules in the protoplasm, and differs from the masked fat in various ways. It varies in amount according to the nature of the food supply. If the food be rich in fat it is more abundantly infiltrated, but if the animal be starved it disappears. In contrast to this, mere starvation does not completely remove the fat which is masked in the tissues. According to Rosenfeld, starvation will reduce the amount of fat in the liver of fowls to about 8 per cent. of the dried tissue. In dogs and other animals a corresponding result is obtained. The persistence of a certain amount of fat in protoplasm has led Albrecht to describe this residue as a permanent fat in the tissues, as compared with the fat which can be transported. The fat especially of adipose tissue is in the form which can be transported. It is enclosed in the protoplasm as a globule, but to all appearance only in the way in which a mass of foreign substance is enclosed. It is not intimately united to the protoplasm, and is no part of the living matter. We have seen how the fat comes to be enclosed by the protoplasm by means of granules. In the kidney in man there is little or no fat of this kind. The fat which is in the tissue is intimately combined, and does not become visible, and its presence can be detected only by methods of extraction. In the liver we have commonly both forms of fat present in the tissue, and sometimes in every cell.

When the kidney suffers from degeneration, fat appears in globules in the epithelium. The toxin, of which the degeneration is an effect, acts on the kidney cell, and destroys its power of retaining fat in its intimate structure. Hence fat appears in a multitude of globules throughout the protoplasm, and takes then the form of merely enclosed fat. The separating of this fat from the protoplasm is the visible effect of the toxin, and the cell which is unable to retain its normal amount of fat combined in the protoplasm, is said

to be in a state of fatty degeneration. There is in this change in the cell neither increase nor decrease in the quantity of fat in the cell. The fat which is already present simply becomes more or less visible in globules.

Since the work of Lebedeff and Rosenfeld on the transportation of fat in relation to fatty degeneration, much attention has been paid to this aspect of the problem. It cannot, however, be said that attempts to reach an explanation of fatty degeneration by this process have been successful. It has, obviously, no application to the case of the kidney, to nerve, to ordinary muscle, and it is very doubtful if it has any application to heart muscle. Further, as Bainbridge has shown, it does not apply to the liver of the cat in the case where he induced fatty degeneration by ligature of the hepatic artery.

In other words, all the phenomena of fatty degeneration do in certain instances occur without any appreciable increase or diminution of the amount of fat in the degenerated tissues.

The pathological aspects of infiltration have never been clearly explained. The patient with phosphorus poisoning shows increase of fat in the liver, and this comes by transportation. But the liver is a tissue which infiltrates fat as part of its normal function, and therefore we may suppose that a continuation of this normal function would explain the accumulation of fat in the cells; for, clearly, degeneration leads to the inability of the liver to combine with fat, and it is in this combined form that fat enters into metabolism. If the liver cell, then, can infiltrate fat, and yet fails in its metabolism, accumulation is inevitable. But does the damage due to the phosphorus necessarily cause the cell to take up the fat at an increased rate? That can hardly be possible, because, if the infiltration were an effect of the poisoning, one would expect the poison to cause it in the non-infiltrating tissues.

We may conclude, therefore, that the accumulation of fat in excess, though it may occur in degenerating organs by infiltration of fat brought by the blood, is not an essential part of the process of degeneration. Degeneration consists solely in the inability of the cell protoplasm to combine with fat in the normal quantity. It may be that there are degrees of this process. It has been pointed out that, in organs of animals which are poisoned with phosphorus while they are in a condition of starvation, there appear in the cells globules of a fatlike substance which stains with osmic acid, but not with Scharlach R. In other words, at this stage a lipoid substance, which in staining resembles the myelin of the nerve sheath, appears; whereas if the cell had not been deprived of fat by starvation, fat would appear as a result of phosphorus poisoning.

By a study of the stages in degeneration we may hope to determine in what sense the fat and lipoid substances are essential and

indispensable elements in the protoplasmic economy. It is clear, however, that from ordinary degrees of fatty degeneration the protoplasm recovers, so that the displacement of fat from its masked condition may take place to a certain extent without causing the death of the protoplasm.

The effect of phosphorus is to cause the masked fat of the protoplasm to appear in visible globules. This loosening of the bond between the protoplasm and its normal fatty content leads later to the occurrence of an excess of fat in the blood, in the form of lipæmia. The direct effect of lipæmia in the tissues which infiltrate fat is to lead to an excessive accumulation in them; this may be seen also in diabetes. Hence we may naturally expect in the liver an excess of fatty infiltration accompanying degeneration of any general kind. Again, there is evidence, though not altogether conclusive, that phosphorus-poisoning decreases the oxidation of metabolism, and therefore also leads to the accumulation of fat. Decreased oxidation, however, clearly follows if the protoplasm is unable to bind fat in normal quantities in the masked form which is the basis of metabolism.

**Hyaline Degeneration.**—While it is still impossible to give a clear definition of hyaline degeneration, we are able to describe it by means of certain well-defined characters. Its presence in any tissue is shown by the deposition in the cells or other structures of a protein substance which gives to the affected elements a glassy homogeneous appearance. Von Recklinghausen pointed out that the best means of recognizing the presence of this substance is to stain the tissue with acid dyes, and treat the stained sections with solutions of acetic or sulphuric acid. By this means the acidophil character of the substance is brought out. It is also refractile in appearance, and in deposits which are of some standing, as in cases of chronic disease, the hyaline substance is very resistant to the solvent action of acids and alkalies, as well as of water and alcohol. It does not stain with iodine, and from this we obtain the readiest means of distinguishing it from amyloid matter. On the other hand, certain of the normal constituents of connective tissue are acidophil, and stain much in the same manner as hyaline substance.

Any strict classification of the forms of the degeneration is impossible, and that which has been adopted is based on the origin of the substance. It includes two chief varieties: (1) Hyaline derived from cells directly, either as a secretion by glandular epithelium or as an accumulation of masses of hyaline substance in the protoplasm of the cells; (2) as material which is deposited from the exudate of inflammation. These two forms are distinguished as secretory hyaline, and coagulation or hæmatogenous hyaline; but it is not in every case easy to say to which of these forms a given example should be ascribed. The occurrence of

hyaline coagula from the blood in the thrombi of aneurisms and endocarditis was described by von Recklinghausen, and subsequent observers have obtained similar results, and in particular the frequency of hyaline thrombi in the capillaries of the brain, in cases of death from infectious disease, has been pointed out. Again, exudative hyaline is frequently found in the pseudo-membranes of diphtheria and in the fibrinous layer which forms on the surface of an inflamed serous membrane, and especially in the deepest and oldest part of it. The hyaline material seen in chronic inflammation of lymph glands and in tuberculous foci is probably also exudative in origin.

Again, hyaline material is deposited in the walls of capillaries, causing thickening, and gradually leading to closure of the lumen, with atrophy and disappearance of the endothelial cells. This change in the capillaries is seen in senile conditions, and also in chronic inflammation, where it extends beyond the vessel to newly-formed connective-tissue fibrils. In these examples it originates chiefly in the endothelium, and may be regarded as secretory in form. It is seen in the connective tissue in fibrous tumours of the conjunctiva, larynx, intestine, etc. It is very commonly seen in the glomeruli in cases of old-standing interstitial nephritis. It is found in sarcomata, either in the vessel walls or in the stroma of the tumour; and, finally, it occurs as a degeneration of muscle, striped or smooth, in heart muscle, in the media of arteries, and in the muscular bands of myomata.

As regards the process by which the hyaline substance comes to be deposited, very little is definitely known. It has been suggested that the substance of hyaline thrombi comes from the leucocytes or the blood-plates, or even from the red corpuscles. Weigert, on the other hand, advanced the theory that we should regard its formation as closely related to the coagulation of fibrin and coagulation necrosis. He points out that in necrosis and hyaline degeneration equally the nuclei disappear, and the remaining tissue shows a well-defined tendency to calcification. Masses of fibrinous deposit may become hyaline; and while diphtheria membrane in the pharynx may be hyaline, it may in the air-passages be fibrinous in the same case. Hyaline thrombi in lung infarcts and hyaline casts in the kidney tubules have been shown in certain cases to incorporate fibrin threads which still stain by the Gram-Weigert method.

In general, the relation of the two processes is at once clear from the fact that they occur under the same conditions. It has been suggested that the conditions under which hyaline forms in fibrinous deposits are those in which the material is washed by an excess of plasma. Hence, also, arises the tendency for hyaline to form in bloodvessel walls, in the tissue of chronic inflammation, and in the stroma of angeiosarcoma.

Von Recklinghausen made an observation of great interest in relation to the stability of hyaline substance. Whereas the substance as it is seen in old-standing chronic formations resists solvents and digestive action, yet the more recent deposits are much less resistant, and much more resemble ordinary proteins. The difference, therefore, between hyaline and soluble proteins, which is at first slight, becomes gradually more defined. We have seen, also, that the hyaline change may occur in fibrin; and Litten has shown that if amyloid substance be placed in the peritoneum of an animal, and retained there for some time, it loses its specific reactions, and comes to resemble hyaline substance very closely.

Coagulation hyaline is an example of the extracellular formation of hyaline, and here it is deposited from the plasma; or, as we have seen, deposits of fibrin may become changed into hyaline. In the secretory variety the hyaline substance is derived from cell protoplasm directly; at the same time dead protoplasm washed with tissue fluids also becomes hyaline.

**Amyloid Degeneration.** — Amyloid degeneration causes in the organs affected, changes in size and appearance which can be easily recognized by the naked eye. The size is increased, and in advanced cases may reach a bulk two to three times that of the normal organ. This increase is due to the deposit of amyloid matter in the connective tissue of the arteries and capillaries, and from the clear, translucent appearance which this substance possesses, the organ affected loses its natural colour, and comes to resemble a wax cast. The appearance of each organ affected has well-defined macro- and micro-scopical characters. In each case the first and chief change is due to the deposition of this substance outside the endothelium of the capillaries, or in the connective-tissue fibres of the media, with atrophy and complete disappearance of the muscle, thickening of the wall, and narrowing of the lumen. The wall, however, still retains, as in the kidney, a remarkable degree of permeability. The damage which amyloid degeneration causes is twofold, since it affects the bloodvessels directly; while by pressure, and in other indirect ways, it affects the cells which these vessels supply. The amyloid substance is distinguished by certain specific staining properties. It gives a mahogany brown with iodine, and if, after the iodine solution has been applied, we add a solution of sulphuric acid or chloride of zinc, in certain cases a blue or violet colour is obtained. This reaction with iodine suggested to Virchow a similarity with vegetable amylaceous structures, and he accordingly substituted the name "amyloid" for the older name "lardaceous." In its general physical and chemical characters amyloid resembles the other colloid substances. It is refractile and translucent, and generally resistant to the action of chemical solvents and digestive ferments. It can, however, be digested both by trypsin and by pepsin, though slowly; and for the

purposes of chemical isolation use is made of the fact that it is soluble in baryta solution. It occurs in large quantities in the liver, and in an advanced case the deposit occupies the greater part of the tissue, leading to the replacement of the cellular and fibrous structure of the organ by masses of homogeneous substance. In addition to the iodine stain, it also gives a characteristic red stain with methyl violet, while the rest of the tissue takes a blue tint; but this stain is generally regarded as of less differential value than that of the iodine, since certain forms of hyaline substance give it also.

Amyloid has been the subject of much chemical investigation. It was, in the first instance, shown by Friederich and Kekule to be essentially proteid in composition, and more recently Krakow has shown that the protein is linked with chondroitin-sulphuric acid—an acid which is a normal constituent of elastic tissue and of cartilage. Amyloid is therefore not only similar to normal constituents of elastic tissues, but is also, as we have seen, closely related to hyaline substance. Cases are described in which in one organ the amyloid reaction is given by the deposit, while in another that of hyaline is obtained; and we have already seen that amyloid subjected to the action of fluids in an animal body loses its specific characters and comes to resemble hyaline. How closely they are related chemically has not so far been determined. Krakow further claimed that from the aorta and other tissues he had been able to isolate a substance very similar to amyloid, which contained chondroitin-sulphuric acid linked with a proteid. Till that result was reached it had been impossible to point to any normal physiological substance which was closely related to amyloid.

Neuberg has investigated the relationship of amyloid substance to the body, which is found in the normal aorta, by comparing the molecular structure of the protein elements present in combination in the two substances. From this study he finds that there is a considerable difference in the constitution of the protein in the two cases, and that the protein moiety of the liver amyloid has the characters of the basic group of proteins to which thymus-histon belongs. Further, thymus-histon is combined with nucleic acid, while the amyloid protein is combined with chondroitin-sulphuric acid; but proteins belonging to this group do not occur frequently in the normal body. The characteristic proteins found in fish ova, on the other hand, belong to the basic group, and of this series the different forms which have been isolated are regarded as arising by a progressive modification of ordinary proteins. Neuberg suggests that the various forms of basic protein which he has found in amyloid liver and spleen, and in the aorta, may be regarded as having a similar relationship to each other. In other words, the variation in amyloid substance arises from a gradual chemical change in the constitution of the protein moiety, the end of the

series being represented by liver amyloid. Finally, Neuberg showed that in its decomposition products chondroitin-sulphuric acid revealed a nitrogen containing acid showing close relationship with carbohydrates.

The clinical conditions in which amyloid degeneration occurs are very various, but of these the most outstanding is chronic suppuration and loss of albuminous material. The following are Hjelmann's results, quoted by Lubarsch: In 189 cases there were 98 lung tuberculosis, 25 bone and joint tuberculosis, while 35 were due to syphilis. Among less frequent causes are cancer, nephritis, leukæmia, Hodgkin's disease, and sarcoma of the kidney. It is perhaps worthy of remark that sarcoma is so little associated with amyloid degeneration, since tumour tissues of this type contain basic proteins resembling those seen in amyloid molecules. Finally, cases have been frequently recorded in which a general condition of amyloid degeneration had been established without any obvious cause.

As regards the time required for the deposition of amyloid, it has been observed in the tissues after suppuration has lasted ten weeks. Usually in slowly-developing phthisis a much longer time elapses before evidence of the deposition can be obtained. It is first seen in the spleen, and then in the kidney. Exceptional cases occur in which the degeneration is confined to one organ—*e.g.*, the intestine. Litten gives an interesting analysis of 250 of his cases. The degeneration was found as follows: Spleen in 99 per cent., kidney in 98 per cent., endocardium in 76 per cent., liver in 65 per cent., and intestinal mucous membrane in 67 per cent., of the cases. On the distribution of the deposit in the various organs, some light has been thrown by the experiments of Davidsohn. It has been shown that the injection of staphylococci and other bacteria will bring about amyloid degeneration. Davidsohn, working on the relation of the spleen to this reaction, found that in mice from which the spleen was excised no amyloid formation occurred, whereas in normal mice about one-third of those inoculated showed the reaction. This matter requires further investigation.

We may sum up the conclusions as follows: Amyloid material consists of a protein molecule linked with chondroitin-sulphuric acid. The acid is similar to one of the normal constituents of elastic tissues. The protein varies in constitution, and is increasingly rich in basic nitrogen as it passes through the transformation by which it comes to the stage represented by liver amyloid. Basic proteins, though not absent from the mammalian tissues, are relatively less abundant, and the presence of them in large quantity indicates an abnormal form of metabolism set up especially by the conditions found in discharging tuberculous and other lesions. It still remains to be determined what definite cause or condition leads to the accumulation of this material in the various localities in which it is found.

Localized deposits of amyloid substance occur in various situations in cases in which general deposition has not taken place. Amongst other tissues, the following afford instances of this: Granulomata, tuberculous or syphilitic tissue, granulation tissue of the conjunctiva, tumours of the air-passages; here the deposit is in the fibrous tissue, and not in the walls of the bloodvessels.

**Mucoid Degeneration.**—We are familiar with the physiological secretion of mucus by the salivary and other glands, and by the large round epithelial cells which are present in mucous membranes. In degeneration, which leads to an excess of mucus in the tissues, two types of structural change are recognized:

1. The connective tissue may become loaded with mucus and fluid, and take the myxomatous form, which is common in embryonic tissues, and is familiar as a structure in the umbilical cord, where it is known as "Wharton's jelly." The cells have an attenuated branching form, with a central nucleus, small in size, while the interstices of the cell branches are filled by a clear fluid. This tissue is known as "myxomatous tissue," and is frequently found in connective-tissue tumours of all kinds, and also in the matrix of myomata and carcinomata. A somewhat rare tumour is met with in subcutaneous tissue, in the heart and elsewhere, which consists entirely of this tissue, and is accordingly called "myxoma." The origin of the mucus which is abundantly present in this tissue has not been made clear, but its similarity to the embryonic connective tissue shows that the change finds analogy in physiological development. In myxœdema the swollen subcutaneous connective tissue contains an excess of mucus in the earlier stages of the disease, and the same change is observed in the tissues of animals from which the thyroid has been removed.

2. The other form of mucoid tissue is that which is known as "colloid cancer." This form of carcinoma is most frequently seen in the alimentary tract, and it may form large secondary gelatinous masses on the serous surface of the viscera in the abdomen. When examined microscopically, the tissue shows that the cellular structure is gradually lost as a result of the swelling caused by the accumulation of mucus, since this change produces not only swelling of the cells, but a complete loss of nuclear and protoplasmic structure.

Mucus appears in a great variety of chemical forms. It is characterized by its power of absorbing water in large quantity. It is soluble in weak alkalies, is precipitated by acetic acid, and remains insoluble in excess. Its composition is that of a protein linked to a carbohydrate, which on separation has the power of reducing Fehling's solution. For the detection of mucus in microscopical sections thionin blue is used in watery solution. This dye tains mucus red, and the rest of the tissue blue.

**Necrosis.**—Necrosis, or death of the tissue, we may look upon as the final stage of the process of degeneration, in which the disturbance of metabolism is so great as to lead to death and disintegration of the protoplasm. In connection with this process we see at work various retrogressive changes, such as absorption of excessive water and swelling of the cell; coagulation of the various normal or abnormal proteid elements of the protoplasm and of the plasma; spontaneous disintegration of the lipoid substances, with the separation of fat, myelin, and protein, from the complex; the solvent action by surviving cells, and by the autolytic ferments which are present in varying quantities in the different tissues.

The process of necrosis therefore varies in different organs, partly because of the peculiarities of the structures affected, and the relative amounts of easily disintegrated and resistant tissue present, and partly because of the effects of the particular cause at work in the given instances.

We may take as an example of the simplest forms of necrosis that which arises when the blood-supply is cut off. This is seen in the organs which are supplied by arteries with little or no lateral anastomosis, and typical instances of this necrosis occur in the spleen, the kidney, and the brain, in cases of embolism from heart disease. In these organs, when an embolus blocks an artery, the wedge-shaped area of tissue supplied by the artery is necrosed, and the area involved is known as an "infarction." In the first stage of the infarction in the spleen we observe that the entire area has become solidified—a condition which Weigert called "coagulation necrosis." The whole of the contents of the area are involved in this process of "coagulation"—the tissue, the blood, the lymph. At first there is a considerable amount of blood in the tissue, including not only that which the vessels contain when the current is arrested, but also that which may come from collateral sources through the small anastomosing channels which exist. In this area of necrosis there is still a certain amount of lymph circulating, with the result that, when the infarction is of small size, the hæmoglobin is gradually washed away, and the infarction acquires the pale characteristic appearance. Subsequently the pale, dead tissue is by degrees removed, and replaced by fibrous tissue, till finally only a small mass of scar tissue is left.

When the infarction is larger, it is to be observed that only a strip at the outside margin of the area is washed free of hæmoglobin, while the central parts have the reddish-brown colour which characterizes retained blood-pigment. Further, the whole of the centre may become soft and broken up by the action of the autolytic ferments which are set free by the death of the cells, and which, since the area is large, are not washed away by the stream of lymph. Hence we often find that the larger infarcts of the spleen have a softened centre, the contents of which, when the

organ is sectioned, flow away like the contents of an abscess cavity.

In the kidney the same type of necrosis occurs, but the kidney's power of absorbing the necrosed tissue in infarction areas is much greater than that of the spleen, and the infarcted matter is removed so completely that in time the site of it is marked by a very small mass of scar tissue at the bottom of a depression on the cortical surface. Here, therefore, the signs of autolysis are much less in evidence than in the spleen.

Again, in the brain the changes met with are chiefly those of autolysis. The area of infarction is an area of softening; the myelin sheath absorbs water, swells up, and softens. From this arise droplets of myelin, which either as such or disintegrated into their constituents—fat, cholesterin, lecithin, etc.—in the form of globules or crystals, and as soluble soaps, are removed from the area by the lymph stream. Some of this disintegrating lipoid passes away, incorporated in leucocytes and other phagocytic cells, and gets transported by the way of the perivascular lymph channels. Another part of the lipoid substance is absorbed by the glial cells at the margin, or by the endothelial or connective-tissue cells which form part of the bloodvessel walls. Finally the whole of the structure is removed, and the area is replaced by a collection of clear fluid, surrounded and retained by a thickened layer of glia. When the area is small, the collection of lymph may finally be absorbed, and the infarct represented by a nodule of proliferated glia.

The changes which take place in conditions of toxæmia with disturbed metabolism are well illustrated by the progress of necrosis in the liver cells in acute yellow atrophy. The liver cell undergoes a process of coagulation, and this is followed by disintegration, which takes place in two stages—(1) that in which the carbohydrate and fatty elements disappear from the cells; and (2) that in which the albuminous constituents are removed. During the first stage, from the liposome granules, from the nucleus, and possibly, also, from proteid combinations with lipoid in the cell substance generally, there appear, even in cells apparently free from fat, droplets of myelin, which, with any fat that may be present, rapidly disappear. After this comes the transformation of the glycogen into sugar, and its disappearance from the cell is closely followed by that of the albuminous substances. The removal of these elements is accompanied by atrophy of the cell, and in the diminution of size we may find a measure of the rate and extent of the removal of the albuminous constituents. The protoplasmic structure is finally represented by a mass of débris of granular appearance, amongst which are granules of bile pigment lying free in the cell or combined with particles of coagulated albumin.

It is important here to observe that the necrosis is more or less

confined to the liver cells. The connective tissue and the bile-duct epithelium may not only survive, but there may be seen to spring from the bile-ducts sprouts of epithelial cells in an attempt to regenerate the lost glandular acini.

In the necrosis and softening of suppurative foci we find more or less similar changes. The presence of a toxin is the cause of the necrosis of the tissue, and from the necrosed tissue autolytic ferments are set free which cause softening and disintegration of the kind just described. At the same time leucocytes are attracted to the focus by the chemotactic toxin, and from the death of certain of the leucocytes further supplies of enzymes arise. Hence, there results in the area of suppuration the process of softening which is in many ways similar to that described in the liver.

An example of necrosis that is frequently not followed by autolytic softening is that seen in the caseation of tubercle. The toxin of tubercle is not positively chemotactic to any marked extent; hence, on examining tuberculous foci we find the centre occupied by a finely granular homogeneous débris of tissue and coagulated protein. Very frequently among the débris are conspicuous granules of lipoid or fatty substance, and, if the area be not too old, fragments of nuclear chromatin, showing that the process of disintegration has proceeded so far, but has been arrested. This arrest of the process of disintegration has been regarded by some pathologists as due to a destructive effect of the tuberculous toxin on the tissue enzymes, and the absence of leucocytes leaves no means of renewal from outside sources. It is to be observed that, when leucocytes from any cause find their way into a tuberculous area, it is rapidly softened. Masses of caseous material may remain without becoming absorbed for long periods, and chemical analyses of the caseous matter have not yet cleared up the reason for the arrest in the process of disintegration which so frequently occurs.

An interesting special form of necrosis is that known as "fat necrosis," which attacks adipose tissue and causes death of the fat cells. It occurs in cases of hæmorrhagic pancreatitis—a condition of inflammation of the pancreas of a severe type, which leads to obstruction of the duct and diffusion of the secretion into the lymph spaces of the gland tissue, and even into the cavity of the peritoneum, so that the fatty interstitial tissue of the pancreas and of the mesentery and abdominal wall shows small irregular areas of necrosis, recognized by their opaque white appearance. On examining these areas with the Nile blue stain, the nature of the change, so far as the fat is concerned, is at once made out. The cells attacked by the pancreatic ferment show that the normal neutral fat has been split up into glycerine and fatty acid, and the fatty acid (oleic acid chiefly) stains blue, while the neighbouring cells which the ferment has not reached give the red stain of neutral fat. This change in the fat is very liable to be followed by calcifi-

cation. Occasionally at an autopsy fat necrosis may be seen in the interstitial tissue of the pancreas apart from pancreatitis, but it is possibly a post-mortem change.

Necrosis occurs also as the result of the poisonous action of so-called "endogenous" poisons. Of this cell the necrosis in the liver which follows jaundice is the best known example.

Corresponding to this are the necroses which occur in the kidney in certain cases of diabetes, in the mucous membrane of the large intestine in uræmia, in the liver and kidney in certain cases of eclampsia.

Necrosis, again, may be due to the action of vegetable poisons, such as ergot, which causes spasm of the arteries and veins, and abrin, which acts in much the same way as bacterial toxins. Corrosive sublimate, on the other hand, is a chemical poison, which sets up necrosis in the intestine and in the secreting tubules of the kidney. Acids and alkalies set up local necrosis by acting directly on the tissues to which they are applied. Similarly, necrosis may be due to the direct action of physical agents—heat, cold, light rays, Röntgen rays, electricity, radium.

Finally, a series of necroses is due to many forms of bacterial poison. These may be either generalized, affecting the secreting cells of the kidney or liver, or they may be localized, as in the focal necrosis of diphtheria. One form of necrosis, known as "Zenker's necrosis," should be mentioned. It is seen in striped muscle when the fibres are converted into homogeneous cylinders of hyaline, brittle material. This condition of muscle fibre is important as an affection of the myocardium in acute toxic diseases. When the patient recovers, the necrosed fibres are absorbed and replaced by connective tissue.

When a mass of necrosed tissue loses its moisture and dries up, it is said to be mummified and in a condition of "dry gangrene." Such bacteria as may be present remain undeveloped, and the dead tissue is gradually separated by a zone of inflammatory reaction, forming a line of demarcation. When the necrosed tissue is moist, it naturally becomes the seat of bacterial changes leading to putrefaction, and it is said to be in a condition of "moist gangrene." When bacteria are the cause of the necrosis as well as of the subsequent putrefaction, the condition is described as "primary gangrene"—for example, cancrum oris in unhealthy children, and gangrenous broncho-pneumonia. When the bacterial changes have arisen as a result of infection subsequent to necrosis due to such a cause as arterial obstruction, it is called "secondary gangrene." An example of this is seen in the gangrene of the strangulated coil of intestine which has undergone necrosis from obstruction of the arterial supply, and then become the seat of putrefactive changes.

**Calcification.**—The process of ossification may be looked upon as an example of physiological calcification. The basis of bone is a

fibrous matrix, and the strands of this become infiltrated with calcareous salts. The fibrous element develops an affinity for these salts, leading to the absorption of them from the surrounding fluids in which they are present in small quantities. The same property is exhibited by cartilage, and very commonly during the senile period of life the hyaline matrix exhibits a hitherto undeveloped tendency to calcification in the costal, laryngeal, and other cartilages.

Pathological calcification is in the first place to be compared with ossification, because the salts deposited in both cases are similar, or even, according to some observers, identical. The two processes may be contrasted, however, in that ossification is of regular structural form, and occurs in normal or healthy tissue, while calcification has a very various formation, and occurs in dying or dead tissue, or even in extruded material.

The affinity for calcareous salts which leads to calcification appears as a part of certain processes of retrogressive change. Tissue which has passed into a condition of hyaline degeneration—as, for example, in old inflammatory scar tissue or in the thickened intima in cases of arterio-sclerosis—shows a well-marked tendency to become calcified. Here the combination with the hyaline substance is probably one of absorption. On the other hand, in the case of fatty tissue, the deposition of calcareous salt is due to the combination of fatty acid with the calcium base. The neutral fat is in the first instance hydrolyzed by ferment action, or even by the action of carbonic acid; and the fatty acid set free combines with the calcium oxide to form calcium soaps, which, being very insoluble, are precipitated. In time the soap is replaced by phosphates and other salts, and the hard, stony mixture of calcareous salts is finally formed. The calcification of extruded matter or of necrosed tissue may be due to either type of affinity, since in both instances there are present albuminoid as well as fatty molecules, which may form the occasion of the deposition.

Another condition to which importance has been attached is that in which the fluids of the body are overloaded with calcareous salts from a disturbance of the calcium metabolism. The saturation of fluids like the lymph or the plasma of the blood with carbonic acid markedly increases their capacity for dissolving calcareous salts, and when the carbonic acid is removed there is, naturally, a deposition of these salts. It has been suggested that by this we may explain the action of osteoclasts. Their activity gives rise to carbonic acid in abundance, and the surrounding fluid, being saturated by the acid, dissolves and removes the calcareous salts. These salts, however, are precipitated in some other part of the body. Hence the condition originally described by Virchow as "calcareous metastasis," in which calcareous salts are removed from the bony tissues and deposited in the kidney and elsewhere.

The experiments on injection of various calcareous salts into healthy animals have shown that when there is excess of these salts in the blood and lymph they are deposited in the normal tissues. This observation has importance, since it shows that mere excess of lime salts in the fluids of the body may lead to calcification in tissues which, apart from this, show no tendency to it. The metastatic is, however, a very rare form of calcification, especially in comparison with that which is found in morbid and in necrosed tissues.

Another form of calcification which is rare, is that which occurs in the protoplasm of the cell. Nerve cells occasionally show calcification, and calcareous granules are seen in the cells of the kidney tubules in cases where there is diminution of the secretion of lime salts by the kidney.

Examples of calcification may be classified according as they are found in dead matter or in tissue where vitality has been diminished merely.

Of the first type we find examples in the calcification of the mucus and epithelial masses of bronchial origin, giving bronchial stones, the fæcal concretions of the appendix, the stones which are found in gland ducts, the calcification of thrombi in veins and lymphatics, in all of which the calcification has occurred in material extruded from the tissue. Closely allied forms of calcification are found in tissues which have undergone necrosis, but remain *in situ*. Examples of this are seen in the calcification of tuberculous foci, in lymph glands, or in the lungs; of the tubules of the kidney subsequent to the occurrence of necrosis from poisoning by corrosive sublimate; of adipose tissue in fat necrosis following pancreatitis; of a lithopædion or calcified fœtus. Examples of calcification associated with diminished vitality are seen in tissues formed as the result of inflammation in pleura, pericardium, dura mater; in the degenerated tissue of the intima or media of arteries; in tissues of tumours; in cartilages during senile life.

The calcareous salts appear in the tissues in the form of fine granules or crystalline particles, and as angular or rounded masses. They may be removed by mineral acids, and these are used to decalcify where a microscopic study of the tissue is desired. Another very convenient method of decalcifying is to add a few drops of formic acid to the formalin in which the tissue is fixed. The masses of calcareous material stain with hæmatoxylin so distinctly that their diagnosis presents little difficulty. Von Kossa has introduced a method of staining calcareous deposits by silver nitrate. The tissues are placed in a 5 per cent. solution till a precipitate of silver phosphate has formed, and this blackens on exposure to light.

The chief constituents of calcareous deposits are calcium phosphate, about 85 per cent.; calcium carbonate, about 10 per cent.; and magnesium phosphate, about 1 per cent.

## CHAPTER VII

# HYPERTROPHY AND ATROPHY

By JAMES RITCHIE

## I. HYPERTROPHY.

Under certain circumstances an increase in the size of some bodily organ or system occurs without there being any essential alteration in its microscopic structure; such a phenomenon is called "hypertrophy."

The most important hypertrophies arise when for any reason there is a call for increased function in any part of the body; often such a call takes place in a perfectly normal individual. To this class belongs the hypertrophy of the uterus during pregnancy, the originating stimulus of which is quite unknown, as the increase in the size of the organ is in anticipation of a future requirement. More intelligible are cases of hypertrophy where increased function is at the time actually being performed—as instance the case of the thickening of the epithelium on the hands of manual labourers or the increased size of the muscles seen in those engaged in continuous great muscular exertion. In other circumstances hypertrophy is observed in consequence of defect in one part of the body throwing increased work on another part; such hypertrophy is denominated *compensatory*. Thus, in certain paired organs of the body, when one is lost the other enlarges and performs the function of the two. The best example is found in the kidney. Sometimes during fœtal life one kidney does not develop, or later it may be thrown out of action by local disease (suppuration, hydronephrosis, injury); the remaining kidney then enlarges and performs the duties usually discharged by the two organs. Similar facts are true of the suprarenals and of the thyroid gland. Again, part of an organ may be destroyed, and the remainder may perform the functions of the whole. Thus, in the case of the liver, three-quarters can be experimentally removed, and the remaining quarter will increase in size. Such an observation throws light on how, when a large part of the organ is destroyed in certain cases of subacute yellow atrophy, the remainder is able to meet the requirements of the body. Again, where in women extreme tight-lacing is practised,

while atrophy of the part pressed on occurs, there is evidence that other parts of the organ hypertrophy. Other examples of compensatory hypertrophy are seen in the enlargement of lymphatic glands when the spleen is removed, in the increase in the cardiac muscle in valvular defects of the heart, in the thickening of the intestinal wall above a stricture, and in the increase in the muscular tissue of the bladder when there is obstruction to the outflow of urine. A specially interesting case is the hypertrophy of the arteries and veins which takes place when a necessity arises for an increased flow of blood to any part of the body, a good example of this being what happens in the ovarian arteries and veins in a large tumour of this organ.

Certain conditions which in structure appear to be hypertrophies are outside the physiological requirements of the body, and are difficult to distinguish from tumours. The best example is found in the enlargement of the thyroid seen in simple goitre; this in structure resembles the normal thyroid gland, except that the acini are more irregular in size and, generally speaking, larger than those of the normal organ. Though the gland may be of great size, it may produce no effects on the body except those of a mechanical nature. Another example of a similar hypertrophy is the excessive formation of leucoblastic tissue in the marrow in leukæmia, which disease is by many looked on as really a tumour.

A particular group of hypertrophies is associated with disorders of internal secretion. Examples of these are the increase of the osseous tissues in acromegaly, and the enormous deposits of fat which are probably associated with some defect in the lipolytic mechanism of the body.

The hypertrophy of any bodily organ may be due to an increase in the size of the individual elements, this being denominated *true hypertrophy;* or it may be due to an increase in the number of the cellular elements, this being called *hyperplasia.* In nearly all cases probably both events occur. The existence of the former can be seen microscopically in the heart; and although the occurrence of the latter is more difficult to prove, it is known to take place in the hypertrophy of the uterine wall during pregnancy, and also in the liver, where mitoses can be seen in liver cells during the enlargement of part of the organ. The degree of functional or compensatory hypertrophy of which any part of the body is capable is a function of the persistent embryonic capacity of the part. Thus, if before birth one of the kidneys is arrested in development, the other may be found to be of the weight of two kidneys. But if one kidney be removed after birth, the weight of the remaining organ rarely exceeds two-thirds of what would be the combined weight of two kidneys; and if one kidney be removed late in life, the other undertakes the whole excretory function without any very marked increase in size. Where a kidney is removed early in life, the

glomeruli and convoluted tubules of the remaining organ increase in size both by an increase in size of cellular elements and by an increase in numbers, and the capillary loops are also apparently larger and richer. The correlation of hypertrophy with embryonic capacity is also seen in the heart, where the capacity for increased function is not indefinite, but ultimately fails.

No account can be given of the actual sequence of events which occurs in either the increase in the size of a cell or in the increased number of cells taking place in a hypertrophying part; it is simply the fact that under conditions of health the bodily tissues are never working at their maximum capacity, and that therefore there is a reserve of potential energy which can be made to meet the exigencies of an emergency. One factor in the process may be the increased blood-supply which a functioning organ always receives, but we know too little regarding the conditions governing cell division to say whether this is the only factor concerned.

There are certain enlargements of tissues which may be denominated "false hypertrophies." Thus, in pseudo-hypertrophic paralysis the changes in the muscles cause an apparent growth in size which is really the expression of a degenerative process. Inflammation, further, occasionally accounts for apparent hypertrophies, especially in the skin and mucous membranes.

## II. ATROPHY.

Following on the fertilization of the ovum, the cells set apart for the formation of the soma have conferred on them capacities for assimilation, growth, and asexual reproduction. These capacities are, however, limited; after a time they begin to be gradually lost, and the condition known as "senility" supervenes. The onset of old age is characterized by progressive loss of appetite and weakness, which is the expression of the loss of the power of taking advantage of the energy of food material. From the structural side the loss of function is found to be accompanied by a gradual diminution in the size of the cellular elements of the body, without very definite change in microscopic appearance, and this is denominated *senile atrophy*. The process affects all the tissues—muscle fibres, ligaments, fasciæ, bone, cartilage, glands (liver, kidney, thyroid), nerve elements, epithelium—and is accompanied by a macroscopic diminution in the size of all the organs. The muscles become small and flabby; the bones are more cancellous, and the prominences for the attachment of muscles less marked; the skin has a glossy appearance, and its dryness and the loss of hair indicate that the special epithelial structures—hair, sweat, and sebaceous glands—are sharing in the general loss of activity. While microscopically the chief change observed is a diminution in the size of cells, there are some special modifications in histological

appearance which seem to be directly consequent on the senile change. Chief amongst these is the flattening out of elastic fibres, a hyaline condition of connective-tissue fibres, and the appearance of pigment in certain of the specialized cells of the body, notably those of the liver and heart. In the last case brown granules develop close to the nucleus to such a degree as to give a brown appearance to the whole of the shrivelled organ—the condition known as " brown atrophy of the heart." That all the tissues are not affected by the senile process to the same degree is exemplified by the fact that the less specialized connective tissues forming the framework of atrophying organs often proliferate in an apparent attempt to maintain the normal shape of the part. A similar event is seen in that cells becoming senile are often attacked by phagocytes and consumed. A special example of such phagocytosis is found in the activity of the osteoclasts, which is responsible for the cancellation of the bones occurring with advancing years. Pure senile atrophy is a relatively rare condition, but it does occur in very aged persons. More commonly the circulatory system fails before the other tissues of the body. In such a case there is widespread endarteritis or an atrophy of the elastic and muscular elements of the media, with the deposit of lime salts in the remains of the structures named and in the connective tissue. The resulting inefficiency of the capillary blood-flow may cause atrophy of the tissues, but the process may be complicated by the occurrence of cellular degenerations.

Senile atrophy is not confined to the somatic cells, but also affects the reproductive elements. This is especially marked in the female, where at the menopause the ova disappear from the ovary (which becomes fibrotic), and atrophic changes develop in the accessory genital apparatus. The uterus decreases in size from an atrophy of the muscular elements, and the fibrous tissue here also increases. In the breast the secreting structures disappear, and their place is taken by fat. In the male the reproductive cells are more persistent, but here also atrophy of the essential testicular tissue occurs with advancing years, and diminution in the size of the organs follows. In all these cases the atrophic cells may become the prey of phagocytes, but in similar processes seen during the metamorphoses of insects cells may simply melt away, and it is possible that such an autolysis also occurs in the senile mammal. The age at which senility supervenes in the human body varies much in individual cases, and occasionally it comes on quite early in life. Much more common is the manifestation of early local senility, of which baldness is an example.

Another group of *atrophic changes includes the disappearance of useless structures*. Such structures may represent relics indicative of the phylogeny of the race ; they may be organs of only temporary utility, or they may be parts of the body which have accidentally

lost their function. Examples of the first class are found in the changes in the primitive branchial clefts and in the modifications which the cartilaginous framework of the face undergoes in the development of the facial bones; of the second, in the disappearance of the ductus arteriosus, the umbilical vein, the thymus gland, and the remains of the Müllerian and Wolffian ducts in the male and female respectively; of the third, in the changes which occur in the acetabulum and the orbit, when the structures normally occupying these cavities are removed. In the last case it is necessary to remark, however, that changes in pressure may play a predominant part in the process. In this group of atrophies there is often a diminution in the size of the cellular elements, and a gradual disappearance of the tissue, the position of which is frequently marked by the presence of fibrous tissue, but, especially where bone is concerned, the gross diminution of the part may be due to phagocytic activity.

Closely allied to these changes are the *atrophies following on disuse of a normal part.* For the maintenance of normal structure periodic function is a necessity. The best example of atrophy from disuse is the flabbiness and decrease in size in the voluntary muscles consequent on lying in bed.

We now pass to speak of *atrophy due to pressure.* Whenever any cell is subjected to undue mechanical pressure, its metabolic and reproductive capacities are diminished. A good example is seen in what happens around a focus of tumour growth in the liver. Here the liver cells become flattened, rectangular and diminished in size without losing their characteristic microscopic reactions. Other examples are found in the thinning of the interalveolar septa of the lung in emphysema, in the atrophy of the kidney substance in hydronephrosis or of the brain in hydrocephalus, in the changes in the anterior aspects of the vertebral bodies when the senile muscular weakness of the erector spinæ alters the direction of the downward pressure of the trunk, in the transverse groove seen on the liver in extreme tight-lacing, in the disappearance of bone in front of an increasing aneurism. The same processes are at work in the artificial prevention of growth in the foot of the Chinese woman, and in the production of the changes in the bones of the skull practised by several savage tribes.

*Atrophy by inanition* may occur, but it is more frequent for cellular degenerations to be found in such cases. A condition closely resembling that of extreme old age may, however, be observed in very slow starvation, such as occurs when for a long period an individual lives habitually on an insufficient diet, especially if little exercise be taken, and a similar result may be seen in certain cases of long-standing malignant disease.

It is stated that sometimes *atrophy of an organ by excess of function* occurs, the examples given being the condition found in

the heart muscle in certain valvular lesions, and the condition of the salivary gland after prolonged exhibition of pilocarpine. This form of atrophy must be looked on as of infrequent occurrence under ordinary conditions, and very little is known regarding it.

An important form of *atrophy is that in which a disturbance of innervation* is concerned. The best example of this is seen in the changes occurring in a muscle following on interruption—either by disease or injury—of its central nervous connection. There is here a marked diminution of the size of the muscle cells, with fibrillation of the myoplasm and proliferation of the muscular nuclei. This leads to a definite diminution of the mass of the muscle. Much less definite are certain atrophies of the skin which have been attributed to faults of a neurotrophic mechanism presiding over this tissue, but the evidence here is quite inconclusive. Similar doubt must be held to exist regarding the part played by nervous influences in the atrophy of a limb following on a paralysis of central origin.

A special type of atrophy is found in the process of *aplasia*—*i.e.*, the premature loss on the part of cells of the capacity of vegetative reproduction. This may be general, as is seen in certain cases of dwarfism; or it may be local, as where a part of the body—*e.g.*, the bones of one side of the face—cease to grow. In the case of the former we may be dealing with some disorder of internal secretion, such as is responsible for cretinism, and, it may be, for the atrophy of the skin and its appendages found in myxœdema. The causes of local aplasia are at present entirely obscure.

From what has been said, it will be gathered that many cases of atrophy are not pure, and pass insensibly into conditions of true degeneration, and it is to be noted that in many degenerative processes (*e.g.*, fatty degeneration of the heart) there is from the macroscopic standpoint a diminution in size of the affected part.

# CHAPTER VIII

# TUMOURS

By JAMES RITCHIE

## The Subject of Tumour Formation defined.

In considering the swellings occurring in the body to which the specific name of "tumour" is to be applied, we are confronted with the fact that to give a scientific definition of a true tumour is at present impossible. We can, however, to a certain extent clear the ground by enumerating the swellings which evidently are not true tumours.

**Swellings excluded from the Group of True Tumours.**—Amongst these are all hypertrophies of organs or parts of organs, whether functional or resulting from disease (*e.g.*, simple goitre); all inflammatory swellings, whether acute or chronic, the latter group including those associated with infective granulomata of known origin (*e.g.*, syphilis, actinomycosis, glanders, etc.). There are also to be put aside the important conditions known as "retention cysts," regarding which a word may be said here.

*Retention cysts* can be formed in connection with the duct of any bodily gland, or with the persistence of ducts arising during early embryonic normal development, which usually disappear during later fœtal life. Examples of retention cysts occurring in normal ducts are found in the ducts of the salivary glands, in the gall-bladder, and in the kidney, and the cause of the blockage is usually the lodging of some calculus in the duct; or part of the duct may become blocked through an inflammatory process taking place in or around some part of its course; or true tumours may obliterate some duct structure.

Examples of retention cysts in persistent embryonic ducts are found in the neck, in the sites of the primitive branchial clefts or the thyro-hyoid duct, in the broad ligament, in the remains of the organ of Rosenmüller, and in congenital cystic kidney.

Retention cysts may attain a large size. Their walls are constituted by layers of fibrous tissue of varying thickness, this tissue in long-standing cysts being formed by the pressure of the swelling irritating the connective tissue normally present, and leading to its

increase. In small and recent cysts the wall consists of the normal lining of the duct, but in old-standing cases the special characteristics of the normal tissue disappear, and the wall is formed of a few layers of flat endothelial cells. The contents of such cysts are largely water, containing a varying amount of albumin, and in addition there may be present, especially in recent cases, material derived from the normal secretion of a gland whose duct is blocked. Thus, in retention cysts of the kidney urea may be present.

**The True Tumours.**—When these swellings of known origin are put aside, there remains the group of true tumours, the characteristics to be looked on as common to all of which are, first, that in all there is a progressive proliferation of cells; and, secondly, that such proliferation does not occur in response to any normal requirement of the tissue from which the tumour springs.

It by no means follows, however, that all swellings possessing these characteristics are alike, either in essential nature or in origin, and it is important at the outset clearly to recognize that the group is indefinite, and may include conditions in which different pathological processes are at work.

Looking at a tumour as the result of cellular proliferation, it is to be kept in mind that during the whole of life multiplication of cells is an important factor in the activity of the organism. Nearly every tissue in the body retains to a certain extent the capacity of multiplication, to which its original development in the embryo was due, although the degree in which this multiplication occurs in adult life varies very much in different tissues. Thus, in the nervous system multiplication of cells probably ceases soon after birth; whereas in the skin it is occurring during the whole of life. The stimuli which call forth this proliferation vary greatly. In exposed surfaces of the body, whether internal or external, the superficial parts are being constantly lost from mechanical causes, and thus wastage has to be made good; and, again, functional decay of cells, such as the blood-corpuscles, necessitates a constant production of a fresh supply. Similar processes are also at work in various glands. The capacity for making good what may be termed "normal wastage" may also underlie certain proliferations occurring when an increased call for functional activity is made upon an organ. Thus, when one kidney is excised, the other kidney enlarges, partly by an increase in amount of functional tissue, and the work of the two organs is for the future done by one. A similar process, in which the occurrence of cell division is more certain, is seen in the liver. Cellular proliferation also takes place when any irritant is applied to the body, or when any breach of surface continuity, as by a wound, occurs. Here it is the connective-tissue framework which specially responds, and the object of the response may either be the destruction of the irritant—for example, a bacterium—or the restoration of the continuity of a wounded surface.

The outstanding feature of normal cell proliferation, however, is that it is strictly subject to limitation, governed by laws of which we are entirely ignorant. Thus, proliferation in a wasted epithelial surface is no more than is necessary to keep that surface at its normal shape and dimensions, and, when a wound occurs, the proliferation ends when the gap is filled up. What occurs in tumour formation, on the other hand, is entirely different, in that here the cellular proliferation is not governed by the limiting conditions imposed on normal multiplication. The essential problems of the pathology of tumour formation are the nature of the special stimuli which start the process, and the reasons for the process being outside normal limitations.

It will clear the ground if we state here the following general principles: (1) That wherever in the body cells are capable of multiplication, there a tumour may arise; (2) that under certain conditions tumours are to be accounted for by the multiplication of cells which do not normally occur in the part of the body where they are present.

## Innocency and Malignancy.

A prominent feature in the life-history of tumour formation, and one which for long has attracted the attention of clinicians, is to be found in the different degrees in which tumours interfere with the vitality and viability of the organisms on which they are growing. In some cases a tumour may be present during a large part of the life of an individual without causing serious inconvenience, while in other cases in the course of a few months vital processes are profoundly modified, and death results. The contrast between "innocency" on the one hand and "malignancy" on the other is thus of a very fundamental character, and, as it is associated with well-marked differences in the pathological processes present, it merits consideration at this stage.

**Innocent, Benign, or Simple Tumours.**—In the case of an innocent tumour, we have essentially to deal with one focus of growth in which the process of cellular multiplication is often extremely slow, and in which increment in size takes place at the peripheral parts of the focus. An important feature is that the tumour formation is sharply marked off from the surrounding normal tissues, and where this line of demarcation exists the surgeon is enabled to shell out the tumour from the part in which it is growing. Tumours of this type are therefore often referred to as being encapsulated. There is, however, no formation of a true capsule, and easy excisability is explained by the occurrence of slight chronic irritation in the surrounding parts, resulting in a zone of loose fibrous tissue being formed which can easily be broken down. If the original focus of growth be removed, nothing is left of the

tumour process, and no further trouble is thus suffered by the individual. It must be noted, however, that in the case of certain conditions usually referred to as tumours—for example, the fibro-adenoma of the breast—the line of demarcation between the normal and the diseased parts is not sharp, and an enucleation of the kind described is not always possible, as coarse finger-like processes may extend into, and be to a certain extent incorporated in, the surrounding parts. The definition of these processes, however, is usually not a matter of very great difficulty, and the complete removal of the tumour is possible. While innocent tumours are characterized by their focal nature, the foci sometimes attain a very great size, examples being found in the fatty tumours developing in the subcutaneous tissues and in tumours arising from the uterine muscle. Although growth in such cases is strictly local, serious effects may be produced by pressure on the surrounding parts, these being pushed aside by the gradually advancing growth, and undergoing atrophy. Life may be endangered by such mechanical effects; thus, in large uterine tumours the functions of the abdominal organs, and it may be of the heart, may be interfered with. Again, innocent tumours of even small size may cause serious results from their relationship to important structures—for example, the brain (as in fibrous and osseous tumours springing from the bones of the skull), and the trachea (as in tumours of the thyroid). Innocent tumours may also endanger life from changes which occur in them. Thus, tumours of the uterus may give rise to congestive hæmorrhage of a serious kind, and in certain cases through superficial ulceration of such growths the path may be opened for the entrance of bacteria which originate pyæmic and septicæmic conditions. Such ulceration is not infrequently the result of the malnutrition of the newly-formed cells characteristic of all tumour formations. In innocent tumours it often happens, especially in the larger masses, that the earlier-formed cells die, and the centre is thus composed of a necrotic mass. When necrosis occurs, there may be observed all the secondary changes produced when cellular death takes place under any circumstances; fatty degeneration and calcification may follow, an example of the latter being frequently seen in the uterine tumours already mentioned.

We have stated that a characteristic of innocent tumours is the fact that only one focus of growth develops. In certain cases, however, a number of innocent tumours may synchronously or successively develop in one individual. Examples of this are found in many fibrous and fatty tumours. The important point here is that these multiple tumours seem to be quite independent of each other, and are the expression of a tendency for new formation to occur in different parts of the body rather than for a growth originating in one part to infect another region secondarily.

**Characters of Malignant Tumours.**—When we turn to consider malignant tumours, we find that clinically as well as pathologically they are differentiated from innocent growths chiefly in two respects. First, generally speaking, their growth is much more rapid, and, secondly, in addition to the original focus, secondary foci tend to appear in other parts of the body. In addition to this, a third outstanding feature of the malignant tumours is the fact that at the peripheral parts there is almost invariably an infiltration of the surrounding parts with extensive, fine, frequently microscopic prolongations, which make it impossible to mark off by any palpable characteristic the growth from the tissues in which it lies. There is very rarely any approach to the false encapsulation which we have noted as characteristic of many groups of simple tumours.

We will consider these characteristics of malignant tumours more in detail:

1. *Rapidity of Growth.*—This varies very much in different cases. Sometimes, as in the case of many malignant connective-tissue tumours—*e.g.*, those occurring in bone—the growth is extremely rapid, and in the course of a few months, or it may be weeks, the tumour may attain such a size as to constitute a very definite proportion of the total body weight. In such a case, as we shall see later, direct microscopic evidence of vegetative activity may be found in the abundance of mitotic figures observable in the cells. In other cases of malignant tumour formation the growth is much more slow, this being exemplified in certain epithelial tumours, say of the lip, and especially in some of the tumours liable to develop in connection with the intestinal mucous membrane. Here there may be evidence of tumour formation being present for many months, in certain cases years, before any gross tumour results. Generally speaking, the connective-tissue tumours are those of most rapid growth, and the epithelial and hypoblastic tumours are the slowest.

2. *Infiltration.*—It is convenient to consider this feature next. As has been stated, the main growths, instead of, as in innocent tumours, advancing by the constant accretion of layers of cells upon the peripheral parts, show a tendency to throw out processes, often extremely fine, in all directions. These permeate the surrounding connective-tissue spaces, and evidence of their existence may exist at a considerable distance from the parent growth. They also frequently follow the lines of neighbouring perivascular lymphatics. If the tumour be slowly growing, the presence of these causes an inflammatory irritation of the surrounding parts, which results in the development of a dense fibrous tissue. Such a development is responsible for the intense hardness characterizing certain malignant tumours—*e.g.*, the so-called "schirrus" condition often found in many cases of cancer of the breast. Some of these clinically scirrhus conditions are, however, due to a dense development of the essential

cells of the tumour. When the growth is more rapid, the irritation produced by the advancing infiltration is of a more acute character, and, instead of fibrous tissue being observed, the infiltration is seen to be surrounded by a well-marked development of plasma cells and of young fibroblasts.

In the case of innocent tumours, we have seen that neighbouring structures may be affected by the tumour mass pushing them aside or pressing on them. In the case of malignant tumours, however, such structures may become seriously affected by a direct continuance of the infiltration into them. The difference in the two cases is well seen in the contrast between what occurs in innocent and malignant tumours of the glands of the neck. In the former case neighbouring structures are simply pushed aside, while in the latter case, arteries, nerves, and veins, the trachea and the œsophagus, may all be infiltrated with the new growth.

The occurrence of this peripheral microscopic infiltration accounts for the difficulty met with, surgically, of completely removing a malignant tumour, as its grossly palpable limits do not represent the whole extent of the tumour formation; and as every part of such a tumour is capable of vegetative activity, further development will take place if the smallest microscopic portion be left at an operation.

This to a certain extent accounts for the so-called "recurrences" which are frequently observed after the removal of malignant tumours. As we shall see later, however, in certain cases recurrence is due to the infection of the wound by cells detached during the operation from the main mass. It may be noted as a further point here, that minute parts left behind at an operation may lie dormant in the tissues, it may be, for many years, and again assume a vegetative activity.

3. *Occurrence of Secondary Growths* (*Metastases*).—Not only is there a widespread infiltration around the original mass of a malignant growth, but cells may become detached and be carried to neighbouring and distant parts, in which they may be caught. Wherever they settle down, they tend to multiply, and new centres of tumour formation are thus formed, these being referred to as "secondary growths."

The paths by which the detached cells travel from the original focus are, generally speaking, the lymphatics and the veins; and while spread by either of these is possible in any tumour, it may broadly, be said that in certain groups of tumours the spread usually occurs by the lymphatic path, while in others the vascular is that which is more commonly followed. Thus, in tumours arising from the external or internal coverings of the body, infection is usually by means of the lymphatics. This is seen in tumours of the breast, lip, etc., and to a certain extent in tumours of the intestine. In such cases the lymphatic glands immediately drainiug the infected part are usually the first to show evidence

of secondary growth. Spread by the vascular system is chiefly in evidence in the malignant connective-tissue tumours of the body. Here it is common to find that secondary growths early appear in the lung, though not infrequently an infection of neighbouring glands may also be observed. The predilection which such tumours show for spreading by the vessels is not at present satisfactorily accounted for, but it may be correlated on the one hand with the fact that these tumours often manifest great vegetative activity, and that therefore the walls of veins may be readily penetrated by the proliferating cells ; on the other hand, an element in the situation may be the necessity on the part of the cells for a particular form of nutrition which they find in the blood, and which may not be present in the lymph. The actual irruption of tumour cells into blood-vessels can frequently be seen in microscopic sections of the periphery of such growths.

It is a question whether the essential factor in metastasis is not the maintenance in cells detached from their point of formation of a capacity for division. An occurrence of this kind takes place in the condition of leukæmia, which, in fact, many pathologists look upon as being, if not a tumour formation, at least closely allied to this group of pathological changes. In the normal history of the leucocyte formed in the marrow, active destruction takes place in the spleen. In leukæmia, where the proliferation of the leucoblasts in the marrow is excessive, not only adult leucocytes, but their progenitors, the leucoblasts, escape into the circulation, and there is evidence that leucoblasts which still maintain their capacity for division settle in the spleen, and there give rise to secondary sources of leucocyte formation.

A third method, by which secondary growths are formed, exists, which is, however, really only a variation of the lymphatic means of spread. This occurs when a tumour infiltrates into some natural cavity, such as the peritoneum. Here direct spread may occur from the point where the serous membrane is first involved, but cells may become detached from the initial point of infection, and, being mechanically carried to other situations in the serous cavity, may settle down and produce widespread growth.

While tumours arising from epiblastic or hypoblastic tissues usually spread by the lymphatics, in certain cases evidence of spread by veins is also found. Thus, in many tumours of the intestine, the probability is that the portal radicals become invaded, for the first site of secondary growth is frequently the liver. A vascular infection is also probably responsible for aberrant cases which are observed, as where in intestinal tumours secondary growths occur in the brain. The apparently aberrant distribution of secondary growths is in certain cases probably accounted for by special nutritive material being essential to the proliferation of tumour cells. Thus, in pigmented tumours originating in the eye, the liver is

frequently the chief site of secondary invasion, and in certain cases the widespread secondary growths of a tumour are found in the medullary cavities, it may be, of nearly all the bones in the body.

Great variations exist in different tumours in the period in the life-history of the parent growth at which secondary infection begins to be manifest, and also in the rapidity of growth of the secondary nodules. In certain tumours of the intestinal mucosa, the primary growth may be in existence for many months before secondary growths appear. On the other hand, in some pigmented connective-tissue tumours, secondary infection may occur within a few weeks of the appearance of the primary tumour. In certain cases the vegetative activity of the cells starting the secondary growth seems to be greater than that possessed by those of the primary tumour. An element which, however, here has to be reckoned with is the fact of the multiplicity of the foci which usually occur in secondary infection, each of a whole group of glands, for instance, becoming affected almost simultaneously. The general result of the operation of these two factors frequently is that very soon the conjoined mass of secondary infections definitely exceeds that of the parent growth. From the biological standpoint the structures of the secondary growth resemble those of the primary. This point will be dealt with later.

**Factors in Malignancy which threaten Life.**—The essential feature of a malignant growth is the fact that it threatens the life of the individual on which it is growing, and we may now look at the ways in which this may come about. Malignant tumours may threaten life, and tend to result in death,—

1. *By the Extent with which the Primary and Secondary Growths interfere with the Functions of Important Organs.*—Mere mechanical factors may come into play, as we have seen is also the case with innocent tumours. But of more importance here is the fact that the infiltration processes occurring in malignant tumours cause an involvement of all parts anatomically related to the primary site of formation. This factor in threatening life thus takes various forms. If the site of the growth is a natural channel—*e.g.*, the larynx, the œsophagus, or the intestinal tract—that channel tends to become blocked, and this alone, and apart from any secondary infection, may be of gravest import. It frequently happens, for instance, that tumours of the intestine come first under observation in consequence of causing symptoms of obstruction of the bowel. Symptoms due to pressure on important organs—*e.g.*, the brain—are also here of importance. And, again, the functions of such organs as the lungs may be seriously impeded by a general infiltration with a growth replacing the functioning tissue.

2. *By Cachexia.*—This term is applied to the gradual weakening of the functions of the organs necessary to life, which tends progressively to increase during the growth of a malignant tumour.

It is not as yet clear what factors are essentially concerned in this process, but the outstanding signs are the gradual loss of weight in the individual, frequently accompanied by a definite anæmia of a secondary type. Though in experimental cancer in the mouse it has been shown that cachexia does not occur without ulceration, it is probably the case that in natural tumours such a depreciation of vitality may occur through the growth *per se*, and without the secondary septic infection which, as we shall see, frequently occurs. Several investigators have studied the effects of the injection of emulsions of malignant tumours (24). In certain cases effects resembling cachexia, with a reaction in the marrow, have been obtained, but in other cases observations have been of a negative character, and at present it cannot be said that there is evidence of the production of definitely toxic substances by cancer cells. We may point out that account has to be taken of the drain to which the body is exposed by the active cell division present in certain rapidly-growing tumours. When such a process occurs under normal conditions, as, for instance, during pregnancy, the call for increased nutrition is met by an increased intake of food. Why this does not occur in persons suffering from malignant disease is not yet evident. And it is proper to say that the necessities of cell proliferation do not account for all the facts, as wasting is often in evidence when the malignant tumour is still small, and where, therefore, active cell proliferation is not a marked feature. In the later stage of many malignant tumours, the occurrence of pain and consequent sleeplessness must be reckoned as an element in the devitalizing process.

From the known facts, it may be deduced that the presence of a malignant tumour in the body produces definite interference with normal metabolism, although we are ignorant of the actual processes at work, of which there may be several operating at the same time. The general conclusion is that the progress of such an interference may alone contribute definitely towards a fatal issue.

A special case of interference by a tumour with a normal process is found in the diminution in the amount of free hydrochloric acid in the stomach observed in cases of gastric cancer. This is probably due to the acid secreted becoming combined with serous exudate from the ulcerating surface of the growth.

3. *All tumours* developing from internal or external surfaces, and tumours originating deeply when these approach a surface, *tend to produce superficial breaches of continuity, the so-called "malignant ulceration."* The occurrence of such ulcers may make for the shortening of life, and that in two chief ways: First, by leading to hæmorrhage, and secondly by opening a path for septic infection. With regard to the former, as we shall see, the blood-supply of a tumour is usually imperfect, and is derived from the normal blood-vessels of the part, or from newly-formed capillaries which develop

as part of the irritative action on surrounding connective tissue—that is, the formation of an imperfect granulation tissue. From the present standpoint, the relations of tumour growths to pre-existing vessels is of the greater importance. The walls of these may, as we have seen, be the site of progressive infiltration, which weakens the elastic and muscular structures present, and easily leads to aneurismal dilatations and ruptures. Hæmorrhages thus readily occur. The extent of these depends on the size of the vessels involved. The amount of blood lost may vary from a more or less persistent ooze, as in many intestinal tumours, to enormous and fatal hæmorrhage, as when the carotid artery or internal jugular vein is involved. The constant loss of small quantities of blood going on, it may be for months, contributes to the secondary anæmia which in any case tends to be associated with malignant growths. Septic infection also frequently plays a part in the effect of tumour growth on the organism, this being marked in tumours about the mouth. In such circumstances the septic process is frequently localized, and is much favoured by the low degree of vitality possessed by tumour cells. Putrefactive organisms thus find abundant pabulum, and render the parts so foul as to interfere with the taking of food. Definite septic infection of parts neighbouring on a tumour may also occur, resulting in septicæmia or pyæmia.

*The relative importance of different factors in causing death by malignant disease* has been investigated by Simmonds (1) in a series of 760 post-mortems on cases of carcinoma affecting all regions of the body. The general results were that death was directly due to cachexia, without further complications, in 33 per cent. of the cases. In other 33 per cent. the cause was some complication directly springing from the presence of the tumour. The main causes of death here were invasions by septic organisms, but in a certain number the cause was hæmorrhage. Amongst the septic cases, a large number were traceable to infections of the pelvis of the kidney or the bladder, especially in abdominal tumours in women. In a further 30 per cent. the fatal result had a less direct relationship with the existence of the tumour,—in nearly nine-tenths of the cases pneumonia being here the cause of death. In the remaining 4 per cent. the carcinomatous condition had no direct relationship to the cause of death.

## Classification and Nomenclature of Tumours.

As the etiology of tumours is still unknown, the basis for a scientific classification is non-existent. Thus, the purpose of any attempt at classification can only be to divide tumours into groups for convenience of reference. All tumours consist of cells whose

appearances and qualities can usually be related to those of some normal tissue. Their outstanding feature is capacity for multiplication, and this manifestation of activity, again, usually reproduces more or less closely the features of the normal development of the normal cells from which they spring. Taking advantage of this principle, it is common to found provisional classifications on the differentiated characters assumed early in embryonic life by the cells from which the body is to be built up. The rationale of such a procedure is that, once the characters of the differentiation are assumed, they tend to be perpetuated whatever change may occur in the destiny of the dividing cell. Certain exceptions to this rule will demand consideration later. Some such simple classification as is given in the accompanying table suffices for the practical requirements of the working pathologist.

The nomenclature applied to individual tumours, based as it is, not on scientific principle, but on usage, is extremely unsatisfactory. The situation must, however, be admitted to be difficult, for tumours of very different clinical portent arise from the same tissue. A large variety of names has thus come into use whose significance can only be learned by experience. Roughly speaking, these names indicate the tissue from which the tumour springs, this being effected by adding the Greek affix *-oma* to the root of the term descriptive of the tissue.

A *papilloma* is a simple tumour of epithelial origin, and the term *epithelioma* is reserved for malignant tumours springing from skin surfaces. The terms applied to innocent tumours springing from connective tissues constitute a large group—a *fibroma* being such a tumour composed of fibrous tissue, a *myoma* of muscular tissue, a *myxoma* of mucoid tissue, a *lipoma* of fat, a *chondroma* of cartilaginous tissue, an *osteoma* of bone tissue. Malignant tumours springing from the same types of tissue are referred to as *sarcomata*. When sarcomata spring from special connective-tissue structures, there is prefixed to the word a term indicating the special tissue—*e.g.*, *myxo-sarcoma*, *chondro-sarcoma*, *osteo-sarcoma*. A simple tumour springing from a gland is usually referred to as an *adenoma*; but the term *malignant adenoma* is often used to designate cylindrical-celled tumours of the intestine. The greatest confusion centres round the use of the word *carcinoma*. This term—the scientific transliteration of the popular word "cancer"—essentially connotes the infiltrative capacity of a malignant growth, and has often been applied to any tumour presenting this feature. According to present clinical convention, however, it is antithetical to sarcoma, and thus indicates malignant tumours of epiblastic or hypoblastic origin, the variety present in any individual case being specified by adding the name of the organ in which it occurs.

## A. TUMOURS ORIGINATING IN POST-NATAL LIFE FROM NORMAL TISSUES OF INDIVIDUAL.

| | Innocent Tumours. | Intermediate Types. | Malignant Tumours. |
|---|---|---|---|
| 1. EPIBLAST: | | | |
| *Skin epithelium* | Papilloma | Simple cystic epithelioma<br>Rodent ulcer<br>Basal-celled carcinoma | Epithelioma. |
| *Specialized epiblastic structures (e.g., breast):* | | | |
| *Skin epithelium* | Adenoma | Adenoma | Carcinoma. |
| *Pigmented epithelial structures* | — | — | Melanotic carcinoma. |
| *Nerve tissue* | Glioma | — | Gliosarcoma. |
| *Germinal epithelium* | Ovarian cyst | Proliferating papilloma of ovary | Carcinoma of ovary. |
| 2. MESOBLAST: | | | |
| *Connective tissue* | Fibroma | Keloid<br>Recurrent fibroma | Sarcoma:<br>Spindle-celled.<br>Round-celled.<br>Small round-celled.<br>Large round-celled.<br>Mixed-celled. |
| | Myeloid sarcoma | — | Myeloid sarcoma. |
| *Primitive connective tissue* | Myxoma | — | Myxosarcoma. |
| *Fat* | Lipoma | — | — |
| *Specialized mesoblastic structures:* | | | |
| *Pigmented cells* | Certain pigmented tumours in animals | — | Melanotic sarcoma. |
| *Bone* | Osteoma: eburnated (adamantinoma), cancellous; odontoma | — | Osteosarcoma. |
| *Cartilage* | Chondroma | — | Chondrosarcoma. |
| *Muscle* | Leiomyoma (fibromyoma) | — | — |
| *Lymph spaces* | — | Endothelioma | Endothelioma. |
| *Lymphatic tissue and blood-forming organs* | Lymphoma<br>Myeloma | ? Certain cutaneous sarcomata<br>— | Lymphosarcoma.<br>Chloroma.<br>Leukæmia. |
| 3. HYPOBLAST: | | | |
| *Intestinal mucosa* | Hypoblastic papilloma | — | Malignant adenoma, carcinoma. |
| *Special hypoblastic organs (liver, pancreas, thyroid, etc.)* | Adenoma | — | Carcinoma. |

## B. TUMOURS ARISING FROM ERRORS OF DEVELOPMENT.

GROUP 1.—Tumours arising from junction of two embryos or from a process analogous to formation of monochorial twins—in either case from cells usually having the capacity of forming more than one embryonic layer.

*From Somatoblast:* Includes many varieties from (*a*) union of two more or less perfect individuals—*e.g.*, Siamese twins—to (*b*) one complete individual plus elements of another (teratoid dermoid cysts, teratoma).

*From Trophoblast:* Chorionepithelioma arising in an otherwise perfect male or female.

*From Combined Somatoblast and Trophoblast:* Usual form—dermoid cyst plus chorionepithelioma.

GROUP 2.—Tumours arising in later embryonic life from displacement of cells which usually are already so far differentiated as to be capable of forming only one type of adult tissue:

| | Innocent Tumours. | Intermediate Types. | Malignant Tumours. |
|---|---|---|---|
| *From epiblast* | Inclusion dermoid cysts | — | Malignant developments in dermoid cysts, branchial clefts or other epithelial embryonic remains. |
| *Special organs* | ? Suprarenal rests | — | ? Suprarenal rests. |
| | Neurocytoma | — | — |
| | Neurofibrilloma | — | — |
| *From mesoblast:* | | | |
| *Bone* | Osteoma | — | — |
| *Cartilage* | Chondroma (parotid, testicle) | — | — |
| *Muscle* | Rhabdomyoma (heart, kidney) | — | — |
| *Bloodvessels* | Angeioma | — | Angeiosarcoma. |
| *Lymphatic vessels* | Lymphangeioma | — | Lymphangeiosarcoma. |
| *Mixed mesoblastic elements* | — | Certain kidney tumours | — |
| *From combined epiblast and mesoblast* | Nævi (moles) | Mixed tumours of parotid | Epithelioma, Melanotic sarcoma, Melanotic carcinoma } developing from nævi. |

## C. PARASITIC TUMOURS ARISING FROM TISSUE OF EMBRYO BEING GRAFTED ON MATERNAL ORGANISM.

| Innocent Tumour. | Intermediate Type. | Malignant Tumour. |
|---|---|---|
| Placental mole | Chorionepithelioma | Chorionepithelioma. |

**The Regions of the Body affected by Tumours.**—Every region and tissue of the body may be the subject of tumour formation, but growths composed of the essential cells of the central nervous system are rare, and may be solely of congenital origin.

It is difficult to obtain statistics showing the relative frequency of simple tumours in different regions and tissues. Simple epithelial tumours, such as warts, occur all over the body, and in the modified epithelium covering the œsophagus and lining the pelvis of the kidney, the ureter, and bladder. Similar papillomata are derived from the intestinal mucosa, these being more frequent in the lower part of the intestinal tract. Simple tumours derived from connective-tissue elements may occur in any part of the body, but they are especially common in the subcutaneous tissues, about the periosteum of bones (including the dura mater), especially near epiphyseal lines, in connection with nerve trunks, etc. In the female, simple tumours are common in the uterus, fibro-myoma being that most frequently met with,—in the ovary, ovarian cysts, fibromata,—and in the breast, fibroma, fibro-adenoma.

Malignant tumours of an epithelial type are most common about the orifices of the body, and the intestinal tumours are of most frequent occurrence at the flexures of the intestine, the sites, in order of frequency, being the sigmoid flexure, the pylorus, the cæcum, and the hepatic and splenic flexures. Malignant tumours are also common about the orifice of the bile-duct. Malignant connective-tissue tumours develop especially in connection with bones, periostia, sheaths of tendons, and intermuscular fascia. In the female the great site of malignant disease is the breast, and occasionally similar tumours occur in the rudimentary ducts frequently present in the male breast.

The following statistics (2) of the assigned cause of death from malignant disease during 1901-1903 in England and Wales may be given as bearing on the site frequency of neoplasms:

*Males.*—33,788 deaths occurred, and the distribution of the tumours in the great sites of tumour formation was given as follows:

| | |
|---|---|
| Stomach | 7,349 |
| Liver | 4,596 |
| Rectum | 3,450 |
| Intestine | 2,385 |
| Œsophagus | 2,107 |
| Tongue | 1,837 |
| Jaw | 1,012 |
| Bladder, etc. | 1,068 |

*Females.*—Total number of deaths, 50,660.

| | |
|---|---|
| Uterus | 11,714 |
| Breast | 8,367 |
| Stomach | 7,119 |
| Liver | 6,935 |
| Intestine | 3,338 |
| Rectum | 2,939 |

With regard to these figures, it is probable that in many cases, where both in males and females death is attributed to malignant disease of the liver, the tumour really originated in some other part of the body, especially the intestinal tract, the liver being a frequent site of secondary infiltration; and with regard to deaths attributed to malignant disease of the uterus, it is probable that a considerable number of the tumours were innocent in character.

**Age Incidence of Tumours.**—Tumours occur at all ages, and this is especially true of those of a simple nature, although here growths mostly appear after adolescence. With regard to malignant tumours, those arising from the internal or external coverings of the body or from glands—those which may be roughly referred to here as being of the cancerous type—are of most frequent occurrence after the age of forty-five. Such tumours may be said to be excessively rare before the age of twenty. Thus (3), out of 5,743 deaths from these tumours in males, only 121 are recorded as occurring before the age of thirty-five; and of 9,070 female deaths, only 262 occurred below that age. Malignant connective-tissue tumours were formerly looked upon as chiefly occurring during the years of adolescence. It is now known, however, that although sarcomata are more common than cancerous tumours in early life, still most examples occur after the age of thirty-five. Thus, out of 860 female deaths, 225 occurred before the age of thirty-five; and of 929 male deaths, 285 occurred before this age. A feature of sarcomata is their relative frequency during the first five years of life. If the average death-rate per million living at each age period be taken, then sarcoma is found to be most fatal in the latest age periods.

**Mortality from Tumours in Different Occupations.**—The following comparative mortality figures for different occupations are given by Newsholme (4):

| | |
|---|---|
| Clergymen | 35 |
| Miners | 36 |
| Medical practitioners | 43 |
| Lawyers | 60 |
| Maltsters | 61 |
| Brewers | 70 |
| Chimney-sweeps | 156 |

The last figure is the most interesting, and will be referred to in connection with the part played by irritation in tumour production.

## The Histology of Tumours.

In treating of this subject it is convenient to provisionally divide tumours into those which are manifestly traceable to the occurrence of congenital defects in the embryo, and those which can be associated with some change occurring in a tissue in post-fœtal life. We shall first deal with the latter group.

**Tumours arising in Post-Fœtal Life.**—The outstanding feature of such growths is that in any case the histological structure conforms more or less closely with that of the tissue from which the tumour arises. Such tumours are divisible into two groups:

1. Those which consist of agglomerations of single cells whose developmental capacities are limited, and whose activities are independent and not correlated to the activities of neighbouring cells in the tumour. To such a simple cellular type the appellation "histioid tumour" is sometimes applied.

2. In the cells of the second group, the divisions taking place in neighbouring cells are so far correlated in that growth results in an attempt to form the unit of an organ; for example, a tumour of the intestinal mucosa may consist of an agglomeration of acinus-like structures. Such tumours are often referred to as of an organoid character.

1. **Histioid Tumours.**—These represent the simplest type of tumour formation, and their development is almost entirely limited to the connective tissues. As is well known, what is usually referred to as "connective tissue" comprises two elements. The first is the connective tissue proper, in which, from a primitive round cell, fibrous tissue, fat, bone, etc., are ultimately built up. In the second, from a cell of similar type, there result cells which are really to be classed as belonging to the blood-forming system of the body. It is with the true connective-tissue cells we have to do at present. In *innocent histioid connective-tissue tumours* the cells closely resemble those found under normal conditions. Thus, a tumour may consist entirely of fibrous tissue, the cells being indistinguishable from those of normal fibrous tissue. In other cases the tumour may consist of fat cells, which only differ from normal fat cells in being larger and more irregular; and, similarly, tumours may be formed of non-striped muscle—tumours of striped muscle almost never occur except as the result of congenital fault, but occasionally striped muscle is observed in a smooth muscle tumour—bone, cartilage, the cells in every case being practically identical with the normal cells of the part.

The cellular structure of such innocent tumours shows great homogeneity—that is to say, there is little variation in size either of the cells or of their nuclei, and their staining reactions are practically identical. One apparent exception in a special tumour may be noted, that of the innocent myeloid sarcoma (so-called "epulis"). This tumour develops usually in connection with the periosteum of the long bones or of the jaws in young subjects, and consists of large multinucleated giant cells embedded in a fairly adult type of fibrous tissue. Cellular elements of this kind normally exist side by side in the situations named, and are concerned in the ordinary development of bone. The tumour may thus be looked upon as derivable from the preliminary elements in bone formation,

and it differs from ordinary simple histioid tumours in that two types of cells are concerned. Generally speaking, its nature is innocent.

On account of the slow growth of innocent tumours, prolonged search is usually necessary before mitotic figures or young cells can be recognized. The edge of the tumour is microscopically sharply differentiated from the surrounding normal parts, and just outside it there is frequently a zone of loose areolar tissue, with outside of this, again a denser layer of fibrous tissue. This latter constitutes the so-called "capsule," to which allusion has already been made.

A different picture is presented by *the histioid malignant tumour*. Here, again, these are chiefly derivable from connective tissues of the body. An outstanding feature is that what very frequently appears to be the most advanced stage of development of which the tumour cells are capable corresponds with a comparatively early stage in the development of a fibrous-tissue cell from the primitive round connective-tissue corpuscle. In normal growth such a cell becomes elliptical, and gradually advances to the formation of the elongated fibrous-tissue fibre. But in malignant tumour formation such an advance may never occur, and the growth may consist entirely of round cells, elliptical cells, or young spindle-shaped cells, these constituting the round-celled or spindle-celled sarcomata which are of frequent occurrence (*vide infra*, Anaplasia). Such tumours often present the appearance of being formed of a mixture of cells, all of which, however, correspond to the younger stages of connective-tissue development, and such tumours are usually described as "mixed-cell sarcomata." A special type of tumour also occurs here, in which at first the cells advance to take the adult fibrous-tissue form, but where, as time goes on, they tend more and more to stop at the earlier stages of development, and finally seem to be incapable of advancing beyond the round-celled stage. Years may elapse before this capacity of advancing to the more adult types is lost. It frequently happens, thus, that a surgeon is called on again and again to remove tumours forming in some particular part of the body, and on each removal the histological picture tends to change from that of a simple fibroma to that of a round-celled sarcomatous type. These tumours are often known as "recurrent fibromata." The association of the presence of an embryonic type of connective-tissue cell with malignancy in connective-tissue tumours does not, however, constitute the only histological characteristic, for there is also frequently here evidence of a departure from the normal in the details of the cell divisions which occur. In the malignant histioid tumours it is usually easy to demonstrate the presence of active mitosis. Sometimes this appears to proceed along normal lines, and the result is the development of cells possessing considerable homogeneity so far as size of cell, size of nucleus, and staining reactions, are concerned. But this is not always the case, and when

aberration occurs it is often associated with special vegetative activity, and consequently with special malignancy.

The aberrations consist in modifications of the process of normal mitosis. In the latter the chromosomes formed are divided into two numerically equal groups, each of which passes to a pole of the spindle and forms the daughter nucleus. In malignant tumours the division of the chromosomes between the poles is often unequal, a majority passing to one pole, and the remainder passing to the other. The result is that, when the cell divides, one daughter cell possesses a nucleus overrich in chromatin, while the nucleus of the other daughter cell contains less than the usual amount. This can be recognized by the existence of differences in size and staining qualities of the nuclei, and the two phenomena are sometimes referred to as *hyperchromatosis* and *hypochromatosis*. Another departure from normal cell division is found in the occurrence of multipolar mitoris. Instead of two attraction spheres being formed in the dividing cell, three or more may appear. The chromosomes formed from the spireme may become equally divided between the poles, or unequally as in the previous aberration. When such a cell divides, a number of small cells, whose nuclei may vary much in chromatic content, may result. These two aberrations account for the great variation in the sizes of cells frequently seen in this type of tumour. Such variations, along with that due to the variability in the chromatic content of the nucleus, are of great significance in the histological diagnosis of malignancy in a connective-tissue tumour. Another feature not infrequently met with is the occurrence of division of the nucleus of a cell without subsequent division of the protoplasm. The result is seen in the presence of multinucleated cells in such a tumour. In passing, here it may be well to insist on the necessity for distinguishing between sarcomata containing multinucleated cells and the myeloid sarcomata already referred to. In this latter type the regularity of the size of the giant cells, and of the spindle-shaped cells amongst which they lie, usually makes the differentiation of the two types of tumours histologically easy.

Such are the chief departures from the routine of normal mitosis which are seen in malignant connective-tissue tumours. Within recent years great attention has been directed to the occurrence of another phenomenon—namely, that of *reduced mitosis*, first observed by Farmer, Moore and Walker (15), in their work on cell division in malignant tumours, and chiefly in carcinomata.

These authors point out that in the body two types of cell division occur: the first, or homo-type division, is characteristic of somatic mitosis—that is to say, of the cell divisions (somatogenic) which go to build up and maintain the ordinary bodily tissues; and the second, of hetero-type mitosis (gametogenic), which is only observed under normal conditions in the preparation of cells for the formation of new individuals. Although it is not essential for the consideration of the subject of the mitosis occurring in cancer, it may

be pointed out that, according to one school of biology, the somatogenic and the gametogenic cells are very early in embryonic life marked off from one another—according to some, even in the first division of the fertilized ovum. According to this view, the soma of the individual may be looked upon as being merely the carrier of the cells relating to the perpetuation of the species. The cells of the individual thus have little to do with the propagative cells beyond providing them with nutrition. This, however, is by the way.

In the homo-typical mitosis characteristic of somatic cells, a certain number of chromosomes, the number being constant in any animal species (in man it is thirty-two), is formed in the equatorial plane of the dividing cell. These are usually V-shaped, and the V's split longitudinally to form daughter chromosomes, each of which passes to a different pole in the spindle of the dividing cell. Each daughter cell thus possesses a number of chromosomes characteristic of the parent cell. From mitosis on this plan all the bodily tissues are built up. In the propagative cells a similar homo-typical mitosis goes on for many generations of cells, but in the maturation of the ultimate sexual cells there is interposed another process, known as *reduced mitosis.*

Different views have been advanced as to the mechanism by which reduction is effected, but the essential fact is that at one stage in the maturation of the reproductive cell a mitosis occurs characterized by the development of only half the number of chromosomes present in homo-typical mitosis. These chromosomes, further, instead of being V-shaped, form figures resembling loops, rings, aggregations of four heads, and so on, and division is not parallel to the spindle thread, but at right angles to it. This reduced mitosis may be succeeded by several mitoses each characterized by the same number of chromosomes. The reduced mitosis is characteristic of both the male and female cell, and when, by fertilization, the male and female nuclei are fused, a cell containing potentially the number of chromosomes normally present in the species is again formed, and in what is now the embryo, succeeding mitoses show the ordinary number of chromosomes.

The relationship of these principles to the histology of tumours, according to the authors named and their co-workers (5), is that a study of the dividing cells of malignant growths reveals in these a very large number of cases where a reduced number of chromosomes is present, the picture obtained being comparable to what obtains in the testicle. In inflammatory conditions, on the other hand, a noteworthy prevalence of reduced mitosis is not present. Whether these observations have any bearing on the intimate pathology of tumour formation must be left for future inquiry.

The appearances at the periphery of a malignant tumour contrast very markedly with what we have described as occurring in innocent histioid tumours. Very occasionally a similar capsulation is seen, but most commonly there is an irregular microscopic infiltration of the surrounding parts with tumour cells. These infiltrating cells pass either directly through the neighbouring connective-tissue spaces, or are seen in lymphatics, especially in those related to the vessels. The walls of the latter are frequently invaded, and small masses of growth may be seen projecting into the lumen—this occurrence opening up the path for actively-dividing cells being detached by the blood-stream and carried to distant organs.

2. **Organoid Tumours.**—We now pass to consider certain points in the histology of organoid tumours. As has been stated, we have here to deal with growths in which a correlation appears to exist between neighbouring cells, the result of which is to cause the growth to imitate some tissue or organ of the body, and here again this tendency is recognizable in tumours of both the innocent and malignant type. A simple example is found in the common wart arising in the epithelium. The cells proliferate, a papilla as a result projects from the skin surface, and becomes dendriform in a very complicated manner, each branch being covered with more or less complete epithelium. Here we have, not a cell proliferating to form a series of cells similar to itself, but a series of cells combining together to form by their growth a tissue in which all the elements of the skin (rete Malpighii, stratum lucidum, stratum corneum) are represented. We have, in fact, a definitely-formed tissue, and not an agglomeration of cells constituting the tumour mass. A similar condition is found in the simple papilloma of the intestine, which essentially consists in the projection from the intestinal mucosa of complex dendriform Lieberkühnian follicles.

Though in innocent organoid tumours the tissues formed are normal in plan, a certain imperfection in attainment is frequently manifest. Thus, in epithelial papillomata the sheet of epithelium is frequently irregular in thickness, and is easily broken through by mechanical influences. The proportion which the different layers bear to one another also departs from the normal, keratinization, for instance, being either deficient in amount, or excessive. When a single glandular tissue constitutes the tumour, the cells may show lack of specialization, and evidence of their being capable of function is wanting. An instance of the former defect is seen in the intestinal papillomata, where most of the cells are of a mucoid type.

In simple organoid tumours, the cells, both in histological appearance and in their mutual relationships, closely resemble those of a normal tissue, and this feature constitutes an important diagnostic point in determining the innocency of a new growth. Thus, in a glandular tumour the nuclei of the cells are usually situated close to the basement membrane, as in a normal gland, and the lumen of an acinus is sharply circular or elliptical.

Amongst malignant tumours, the organoid picture is met with. Thus, in cancer of the breast an acinous tendency is frequently a prominent feature, and in some cases the whole tumour is distinctly glandular in plan. An even more striking example of organoid tendency is found in malignant tumours of the intestine. Here secondary growths in the liver often consist of agglomerations of cells arranged in crypts closely resembling the Lieberkühnian intestinal glands. In organoid malignant tumours the individual cells depart histologically from the parent type to a much greater

extent than is the case in the simple organoid growths, and, usually speaking, it is only their mutual relationships which suggest an origin from an organized tissue. Variations from the normal are of the same types as those already described in connection with malignant histioid connective-tissue tumours. There are great variations in size and shape, and in amount of chromatin present in the nucleus, but, generally speaking, a multinucleate condition is not a prominent feature. Even in the arrangement of the cells, tumours of this class tend to depart from the normal to a greater extent than innocent tumours. For instance, in an intestinal tumour, instead of the cells being regularly set on a basement membrane and forming definite crypts, several irregular layers of cells may be observed, and there is a tendency for blocks of proliferating cells to penetrate from the wall of the crypt into subjacent tissues, and thus to constitute solid infiltrating masses of a very irregular shape, with only here and there a space suggestive of the lumen of a gland. In all such tumours, too, there is a tendency for the organoid character to be entirely lost, and for a histioid character to appear. Thus, in such tumours as cancer of the breast or intestinal carcinoma, the tumour may essentially consist of solid blocks of cells set in a more or less abundant fibrous tissue. If the latter predominates in a tumour, it gives a hardness to the mass usually referred to as a *scirrhus* condition, and if, on the other hand, the tumour cells constitute the chief elements in the growth, the latter is often soft, and is then denominated a *medullary* cancer. There is no difference, however, in essential pathology between the two varieties. Frequently the cells of the secondary growths of an organoid tumour show less capacity of differentiation than those of the primary. Thus, in secondary tumours developing from the skin, there is very rarely any evidence of a capacity for keratinization.

When organoid tumours spring from free surfaces of the body, they manifest a histological picture strikingly different from that present in simple tumours. It has already been noted that a wart consists of a growth of dendriform papillæ away from the free surface. In the commonest malignant tumour of the skin, the epithelioma, precisely the opposite occurs, and there is a dendriform epithelial growth down into the subjacent structures. Thus, in these downward prolongations the keratinizing cells occupy the innermost parts of the finger-like processes; and when these are cut across in a microscopic section, the keratinized cells form what are known as "cell nests" (from the concentric structure presented in transverse section of a cylindrical infiltration). Similar facts are true of tumours springing from such internal surfaces of the body as the intestinal mucosa.

In the case of malignant tumours the secondary growths usually conform closely in histological structure with the primary, this statement being specially true in relation to histioid tumours, except

those characterized by pigment formation, where the secondary growths may be less pigmented than the primary. In many organoid tumours the organoid character is also reproduced in the metastases; for instance, as already stated, malignant adenomata of the intestine frequently show acinous secondary growths in the liver. Sometimes, however, the metastases are composed of cells less highly developed than those of the parent tumours, secondary epitheliomata, for instance, only rarely showing keratinization

**Anaplasia and Metaplasia.**—In connection with the general histology of malignant tumour formation, considerable attention has been directed to the occurrence of two processes which represent departures from the lines followed by cells undergoing normal multiplication. Under ordinary circumstances an embryonic cell in a tissue conforms in its growth to a type characteristic of the tissue to which it belongs, and the cell gradually develops from the embryonic state to a fully adult condition. This is best exemplified in the skin. In this tissue mitosis occurs in the somewhat undifferentiated cells of the deep layer of the rete Malpighii, and as growth advances the cells pass through the prickle stage, and gradually assume the squamous keratinized form found in the superficial layers of the skin. Again, in the trachea, mitosis occurs in the round cells next the basement membrane, and these gradually assume a columnar shape, and emerge on the surface as ciliated columnar cells. Such a process may be modified in tumour formation in two ways.

First, the dividing cell may tend never to assume the adult stage. It advances a certain way towards its natural goal, and then development stops. This occurrence is usually referred to as *anaplasia*. Thus, in the case of a tumour arising from columnar epithelium, no fully-developed columnar cells may appear, the most advanced cells in the growth being of elliptical or irregularly polyhedral shape, the appearances thus resembling the earlier stages of normal development. Such an anaplasia accounts for many of the cellular appearances seen in malignant tumours. It occurs in connective-tissue tumours, especially in round-celled and spindle-celled sarcomata. It is also common in epithelial tumours—*e.g.*, in breast tumours, in rodent ulcers and the basal-celled cancers generally. In these last there is ordinarily little tendency to the formation of prickle and keratinized cells, and the growth consists entirely of cells resembling those of the deep layer of the normal rete Malpighii.

The second type of departure from the normal lines of cell development consists in a cell in its growth not conforming to the type characteristic of the tissue, but tending to follow a type belonging to an allied tissue which may have an embryological relationship to that from which the tumour springs. Thus, the nasal cavities are normally lined by columnar epithelium, which, how-

ever, in tumours in this region may become transformed into squamous epithelial tissue. This is traceable to the cells which are responsible for the growth, instead of following the normal type, taking on the developmental characteristics of the skin epithelium, from the infolding of which in the embryo the nasal cavities are formed. Such an occurrence is known as *metaplasia*, and many other examples of this are known. Thus, typical epitheliomata may spring from the secreting tissue of the breast, which in development is again an infolding of the skin epithelium, or true bone may be found in a connective-tissue tumour not originating in bone. Similar metaplasias where the perversion is to a type of tissue more remotely connected with the primary type have been recorded, and are rather more difficult to explain. An outstanding example is found in the squamous-celled carcinomata of the gall-bladder. It is evident that the relationship of the epithelium lining this structure to that of the skin is somewhat remote, and involves the taking on by one of the primary sheets of embryonic tissue—namely, the hypoblast—of the characteristics of another great embryonic sheet—namely, the epiblast—and many would look on this occurrence as explained by the accidental inclusion in the hypoblast of part of the epiblast. In the lower forms of animal life, however, cases are known where, if a hypoblastic structure be removed, a new structure derived from the epiblast takes its place. Thus, Janeway (6) points out that in Lumbriculus, when the head is cut off, a new head is regenerated; but this head is developed from the endoderm, while in ordinary growth the original head arose from the ectoderm. Although it is difficult to draw conclusions from what occurs in lowly-specialized animal forms as to the capacity for the transformation of hypoblastic structures into epiblastic in highly-specialized mammalia, it is to be noted that such metaplasias as those which occur in the gall-bladder are rare, and might thus be looked upon as excessively aberrant. On the other hand, the tendency amongst zoologists is rather to depart from the view that a sharp line of demarcation exists between the characteristics of epiblast and the hypoblast.

From the standpoint of pathology, metaplasia is by no means uncommon as the result of inflammation. Thus, in the nasopharynx, which is normally lined by ciliated stratified epithelium, it is not uncommon to find in inflammation a transformation into a keratinized type, in which even prickle cells may occur, and a similar transformation is occasionally seen in the trachea in cases of chronic bronchitis and tracheitis.

**The Stroma and Blood-Supply of Tumours.**—Most tumours, besides the essential tumour cells, contain a certain amount of fibrous tissue—the *stroma*. This varies very much in amount, being scanty in rapidly-growing histioid tumours, and most marked in the scirrhus type of cancer. It is derived from the connective

tissue of the part from which the tumour starts, and its development can be best studied in the scirrhus cancers alluded to. Here where invasion is active there can be seen proliferation of connective-tissue corpuscles and leucocytic invasion, the reaction being that present where any chronic irritation, of whatever origin, is present in the body. So marked is this reaction that its presence can be taken advantage of for tracing an infiltrative process, as frequently only a few tumour cells which might easily escape notice are surrounded by a very definite agglomeration of connective-tissue cells. Where the advance of the tumour is slow, an opportunity is given for definite amounts of fibrous tissue to be formed. There may also occur, as in granulation tissue, the formation of new capillaries, but there is no evidence of vessels of higher organization being generated. If, however, the tumour occur in an organ richly supplied with small arteries, these may undergo extreme hypertrophy along the lines obtaining in any other contingency where an organ requires an increased blood-supply.

We shall see, when dealing with experimental cancer in animals, that a phenomenon of great interest and importance sometimes occurs—namely, this, that the connective-tissue reaction may become transformed into a sarcomatous formation. It is probable that from time to time a similar transformation of the stroma occurs in cancers naturally arising, and this may account for the cases where, in a person suffering from cancerous disease, a sarcoma of neighbouring or distant parts may also be observed.

Having thus considered the general histological character of tumours, we may now proceed to take up some of the special features observed in certain cases, and it is convenient here to consider tumours in relationship to the three primitive embryonic sheets of tissue from which the organs of the body are developed, as the tumours of the epiblast, hypoblast, and mesoblast manifest characters correlated with the embryonic capacities of each of the primitive divisions of the embryo.

**Tumours derived from Epiblastic Structures.**—Tumours springing from epiblastic structures present a greater variety than those derived from the other embryonic layers, this being especially marked in tumours arising from the skin and its appendages. In these last the complexity is traceable to three factors:

First, there are derived from the epiblast a number of tissues which in their constitution present considerable differences from one another. Thus, (*a*) there is the skin, in which keratinization is an essential feature; (*b*) in the nose there is a ciliated columnar epithelium; (*c*) in the pharynx and œsophagus the stratified epithelium has simpler structure than that of the skin, and closely allied we have the epithelial lining of the bladder. All of these tissues are derived from similar embryonic cells, which show great differences in ultimate structure.

Secondly, in all of these cases the stages through which the cells pass to reach their adult form are more complicated than those obtaining in the development of structures derived from the hypoblast.

Thirdly, there are developed in connection with epiblast a greater number of specialized structures, examples of which are found in hair-follicles, sweat-glands, and in such an extremely complicated organ as the breast. It is thus easy for the perversions of cellular activity which result in tumour formation to present a greater variety of forms than is found in tumours arising from the other embryonic layers.

To look first of all at the *simple tumours arising from epithelium*, we find a number of varieties. The commonest examples are the cutaneous warts, which, as has been said, essentially consist of dendriform growths of the superficial papillæ of the skin, and which in different examples show variation in the relative proportions of cells representing the deeper and more superficial elements in the normal skin. Special examples of such papillomata are found in corns, in which there is down-growth of a core of epithelium into the deeper layers of the skin analogous in many respects to an epithelioma, but which only excessively rarely shows any tendency to assume the malignant characters of the latter tumour. Similar warts occur in such modified epithelia as those lining the larynx and also the bladder. The histological structure in each case is similar to that of the skin wart, only modified by the absence of keratinizing cells, and in the larynx there is evidence that not infrequently these become transformed into epitheliomatous growths.

The *commonest malignant epiblastic tumour* is the epithelioma. In its typical form, as already stated, a dendriform down-growth of the superficial epithelium takes place. The older cells tend to undergo keratinization, so that the central parts of the invading epithelial processes are formed of cells similar to the superficial cells of the skin, and these processes, when cut transversely, present the appearances of the cell nests which are very characteristic of this type of growth. Sometimes the processes undergo almost complete keratinization, but the keratinized core may be surrounded by cells similar to the other layers of the rete Malpighii.

Many variants of this commonest type, however, occur. Thus, there are conditions which it is difficult to distinguish from a local hypertrophy of the skin, where it may be a number of large papillæ, with no fine dendriform offshoots, penetrate for some distance beneath the skin surface. There may be a little tendency to central keratinization in these down-growths, and at the edge there can be seen a gradual transition to papillæ of normal size. If such growths are true tumours, they are of a low degree of malignancy. At the other extreme we have the most widespread infiltration with cellular processes, which may show little tendency

to central keratinization. The cells composing these processes are irregular in size and shape, have often a large vacuolated nucleus, poor in chromatin, and some individuals tend to spread themselves out so as to resemble superficial skin cells, and may individually show keratinization. Such tumours constitute the most malignant group of epitheliomata.

The other important group of epithelial tumours comprises the *basal-celled cancers* (17), the commonest examples of which are the *rodent ulcers*. The outstanding character of the group is absence of keratinization. Rodent ulcers may originate in any part of the skin, but are specially common about the root of the nose, the external angle of the orbit, the side of the cheek, and the forehead. In histological structure they manifest some variation, but in their most typical form consist of large blocks of somewhat elliptical, closely-packed cells, resembling those of the deeper layers of the rete, the outermost being, as in the case of the rete, frequently definitely columnar in shape. These blocks of cells are usually large, and their peripheral prolongations tend to be definitely marked off from the surrounding connective tissue, and to be devoid of the microscopic infiltration characteristic of more malignant growths. Usually the whole tumour is constituted by cells of the same type, there being little tendency to irregularity in shape or size, and usually there is no tendency to keratinization. Tumours of this kind are, however, sometimes met with in which a slight tendency to cell-nest formation can be detected in certain parts. The rate of infiltration of rodent ulcers is very slow, and such tumours may be in existence for years without attaining any great size. Metastatic growths are excessively rare, and their chief serious feature is that, as the tumours frequently lie in close contiguity to bone, the complete removal of the infiltrating edge may be a matter of great difficulty. In this way the bones of the face or skull may become involved in a widespread local process, which may ultimately lead to death through the occurrence of some secondary pathological process—for example, meningitis. Various views have been held as to the origin of rodent ulcers, this having been traced by different authors to the deep layers of the skin, the hair follicles, the site of sebaceous glands, the place of junction of the duct and secreting tissue of such glands, etc. The justification for suspecting a glandular origin lies in the not infrequent occurrence of spaces in such growths suggesting glandular structure. There is, however, little histological evidence in support of the view, and the spaces may be seen to be filled with cellular débris, or even with blood.

Tumours of the basal-celled type may occur elsewhere than in the skin—*e.g.*, in the breast—and in such circumstances are difficult to differentiate from the endotheliomata.

*Other types of epithelial tumours* of greater or less malignancy also

occur. Sometimes in epithelial down-growths there is an apparent development of cysts, the walls of which are formed by sheets of poorly differentiated epithelial cells whose origin can be traced to neighbouring superficial parts or to sweat or sebaceous glands. The contents of the cysts may be degenerated cells, unformed débris, or sometimes they apparently may contain lymph. These so-called *cystic epitheliomata* are really of a benign character.

*A specially interesting and important group of epithelial tumours are those which follow on, and no doubt result from, long-standing irritation of the skin—e.g.*, by X rays (16) or by working in paraffin oil. Such agents in the first instance produce a chronic dermatitis, with lymphocytic exudation into the chorium, accompanied by a punctate hyperkeratosis, and succeeded usually by an atrophy of the skin. Foci of hyperkeratosis sometimes, however, are extremely persistent, and lead to an epitheliomatous development of an ordinary type.

Looking at tumours arising from the non-specialized structures of the epiblast, we may thus recognize two chief types—first, that in which the cells tend to assume the forms characteristic of the superficial layer (prickle cells, keratinized cells—*e.g.*, ordinary epithelioma); and, secondly, those where the cellular picture conforms to what is found in the deep layers of the skin—the basal-celled type. From the standpoint of strict histological evidence, observations on very early cases leave no doubt that the tumours originate actually from the skin epithelium. In many cases it is impossible to draw a sharp line of demarcation between the normal parts of the skin and those in which the tumour formation has begun, and there is evidence that not infrequently several foci of tumour growth may originate from neighbouring parts of an epithelial surface. In this connection it is also important to note that the tumour formation may creep along hair follicles and the ducts of sweat-glands in a manner which suggests a gradual perversion of the special cells going to form these organs. In certain early cases, studied by serial section, the growth seems to originate in an epithelial focus lying beneath, and unconnected with, the superficial epithelium, and it is such facts support the theories attributing tumour formation to the persistence of embryonic residues. The significance of these will be discussed later. It may be stated that cases are recorded where multiple foci of malignant epithelial tumours have occurred simultaneously in different parts of the body.

The *specialized structures of the skin are also liable to tumour formation*. Thus, simple adenomata occur in the *sweat* and *sebaceous glands*. In connection with the latter there is also the simple atheromatous cyst, which, however, in most cases may be looked upon as a retention cyst, although occasionally the constitution of the walls of such formations shows evidence of an adenomatous proliferation having occurred.

*Simple tumours* also develop *in the breast.* With regard to the commonest of these, the so-called "fibro-adenoma," considerable controversy has arisen. This tumour consists chiefly of connective tissue, usually fibrous, sometimes myxomatous, in which are embedded a number of usually dilated ducts resembling those of the resting breast. There may also be a varying proportion of acinus-like tissue. The tumour is often not sharply marked off from the surrounding tissue. The points at issue are as to whether the condition is to be looked upon as due to a neoplastic proliferation of both the supporting and secretive tissues of the organ, or to a neoplastic connective-tissue change with a simple irritative proliferation of the gland, and whether the changes cannot be accounted for by a chronic inflammatory process involving both elements of the breast which appear in the tumour. The histological evidence is rather in favour of the tumour being of a simple neoplastic connective-tissue character. In a special type (the intracanalicular fibroma), whose characters support this view, there appear masses of myxomatous connective tissue pressing from all directions towards the lumen of a duct, which thus assumes a definitely stellate shape.

True simple adenomata of the breast, however, occur, and here there is a variety which forms a link between such tumours and the malignant neoplasms of the organ. In this, the chief feature is the presence of ducts into the lumen of which there project dendriform, papillomatous excrescences which indicate a special vegetative activity of the lining cells. Such tumours not infrequently at a later date assume a malignant form.

*Malignant tumours* also arise *in connection with specialized skin structures*—for instance, the *sweat and sebaceous glands*—but the most important examples of this group occur in the *breast.* Here there is every variety, from the less frequently occurring adenocarcinoma with a definite organoid structure to the more common, histologically less specialized, and therefore anaplastic, type found in scirrhus and medullary tumours. In these the organoid character is largely lost. The tumour consists of blocks of cells which histologically present considerable differences from the normal cells of the organ. A careful examination of such tumours frequently reveals the presence of an attempt at acinus formation, which shows the tumour to be derived from secreting tissue. These tumours occur chiefly when the breast is undergoing its normal involution—that is, between the ages of forty and fifty. When the breast is the seat of malignant disease at an earlier age, the cells sometimes present a vacuolated appearance resembling that seen in lactating cells, and this can be accounted for by the neoplastic perversion having taken place when they were capable of functional activity.

In breast tumours from time to time a metaplasia occurs, and true epitheliomata may develop from a secreting part of the gland.

A special case of tumours originating from the epiblast is found

in the *ovary*. In this organ during development the "egg-tubes," formed of epiblastic germinal epithelium, grow down into the mesoblastic constituents of the ovary and enclose the ova. In later life a variety of tumours springs from those cells. The most common is the benign cystic tumour—the ovarian cystoma—formed of a complicated agglomeration of cysts lined by columnar or subcolumnar epithelium. The degree of proliferative activity taken on by these cells varies. Most commonly the cysts are large, with but few papillomatous excrescencies from the walls, and, however large they may be, the resulting tumours are essentially innocent in character. In other cases the cysts are usually smaller, the walls show more complicated dendriform projections into the cavities, and the so-called "proliferating papillomatous cyst" results. Vegetative activity is here marked, and if such a cyst be ruptured into the peritoneal cavity, multiple tumours are formed from the freed cells grafting themselves on the peritoneal surfaces. Secondary growths may take place, or death may occur from obstruction or cachexia. From the same type of cell histioid malignant growths of a scirrhus type may originate.

Another group of epiblastic tumours are those arising from the *neuroglia*, or supporting framework of the central nervous system. These gliomata histologically resemble the tissue from which they spring, and consist of cells of the spider-cell type. They are slow-growing and usually innocent, but of course produce serious effects from their position. A type in which greater vegetative activity is manifest, along with less cellular differentiation, is described under the term "gliosarcoma," and these are looked upon as possessing a malignant tendency. Other tumours springing from the central nervous system are probably of congenital origin.

From the epiblast there also arise *tumours of a pigmented character*, which, like the pigmented mesoblastic tumours to be described, are of high malignancy. Pigment normally occurs in epiblastic structures in pigmented cells of the retina, and also in the basal cells of the rete Malpighii, and tumours may arise from either of these tissues. Such a source for pigmented tumours, however, accounts for only a small proportion of such growths in the body. They usually present the appearance of large oval or elliptical pigmented cells, fairly regular as regards shape and size, with a large vacuolated nucleus and with pigment in the protoplasm.

**Tumours derived from Mesoblastic Structures.**—As has already been indicated, the *tumours springing from the connective-tissue elements in the body are usually of a histioid character*, whether they belong to the group of simple tumours arising from any connective-tissue structure in the body, or to the sarcomata which represent the malignant mesoblastic tumours.

In the latter group, where such tumours arise from mesoblastic cells having a special function—as, for instance, the formation of

bone or cartilage—the predominating cellular type corresponds to that seen in tumours arising from non-specialized connective tissue. But not infrequently in specialized tumours the cells tend, even when perverted, to exercise their normal function, and thus in an osteosarcoma, for instance, we have the formation of imperfect bone. This might be looked upon as the result of the stimulation of normal osteoblastic cells included in the tumour, the incident corresponding to the inflammatory reaction which originates the stroma of an ordinary tumour. While such a stimulation may occur to a certain degree or in certain cases, the fact that the formation of bony structure is actually due to the tumour cells is shown by the fact that in metastases in the lungs in such cases bone is not infrequently present.

Generally speaking, in the ordinary connective-tissue tumours the tissue which has been at fault can be recognized and the structure of the growth can be explained. There are, however, groups which present many difficulties. The first of these arises in connection with the tumours denominated *endotheliomata* (18). This term is applied to certain tumours arising especially in connection with such serous membranes as the pleura, the dura mater, and the carotid gland, but similar growths have been recorded in very various parts of the body, especially in connection with lymph and blood channels. In fact, they apparently may originate in any situation where connective tissue may assume a somewhat stratified character in consequence of forming a lining to some potential cavity. The characteristic of the group which in the most easily recognizable forms marks its members off from ordinary connective-tissue tumours is that, instead of the tumour having a frankly histioid structure, the cells tend to group themselves together so as to suggest an attempt at the formation of a membraneous structure. There may thus be developed irregular sheets of cells sharply marked off from, and embedded in, a connective-tissue stroma, which in its amount contrasts pronouncedly with the scanty provision of such tissue present in ordinary histioid connective-tissue growths. There also not infrequently develop spaces sharply lined by flattened cells, which sometimes contain blood (hæmangeio-endothelioma) or lymph (lymphangeio-endothelioma). The individual cells constituting the tumour are spindle-shaped, polyhedral, or squamous, and show no intermingling of stroma cells. Thus, in many cases they conform in structure very closely to certain basal-celled epitheliomata, and it is this analogy which has originated the name applied to the group. Such tumours also resemble the basal-celled epitheliomata in often manifesting a low degree of malignancy.

On the other hand, these growths are often difficult to differentiate from the sarcomata. From time to time in the latter, especially, we think, when these spring from bone, and sometimes especially

in the secondary growths of such tumours, appearances somewhat resembling those found in, for instance, pleural endotheliomata are observed. A special variety of the endothelioma is the *perithelioma*. Here we have a tumour in which elementary vessels possessing a more or less normal intimal coating are surrounded by a sheath of spindle-shaped or polyhedral tumour cells resembling those of an endothelioma. True examples of this tumour are excessively rare. Occasionally the cells comprising them show pigmentation.

Views as to the genesis of the endotheliomata might be complicated by taking into account the opinion of some embryologists that the serous membranes of the pleural cavity, etc., are really of epiblastic origin, and tumours springing from them might thus be regarded as a special type of epithelioma. The occurrence of tumours of this type in other parts of the body, especially in connection with the vessels, would, however, not thus be accounted for, and it is the most reasonable view to look on the special characters of the endotheliomata as due to mesoblastic cells, manifesting, when bounding a free surface, a tendency through metaplasia to assume the characters of epithelial cells whose normal function is to limit the surface of the body. From the epiblastic side we have in the crypts of the tonsils epithelial cells coming closely to resemble the mesoblastic cells covering, for example, the lung. We have thus a common type of limiting cells of extremely simple structure which may arise either from the epiblast or the mesoblast. The possession of common tendencies in tissues of such different embryonic origin may thus account for mesoblastic cells taking on the organoid tendency seen in the endotheliomata.

Another group of tumours which are rather difficult to define are the *melanotic sarcomata*. This largely arises from the different embryonic history presented by the cells originating pigmented tumours. We have already referred to the melanotic carcinomata, and have still to consider pigmented tumours arising from cutaneous moles. Pigmented mesoblastic cells are found in the choroid and the iris, and the latter situation is the commonest starting-point for a melanotic sarcoma. The cells of the tumour are generally oval or spindle-shaped, and present a varying amount of pigment, which is also found free in the intercellular spaces. In certain of the lower animals, notably in the horse and dog, innocent pigmented tumours of a fibrous-tissue type are not uncommon, and arise from pigment carrying connective-tissue cells. We cannot express an opinion as to whether in man any of the melanotic sarcomata seen in parts of the body other than those mentioned above can have a similar origin. The melanotic tumours are usually (but not invariably) excessively malignant. Secondary growths may occur before the primary nodule has attracted the patient's attention; their chief sites are the internal organs, especially the liver and lungs, and their mass may be very great.

Another group of difficult *mesoblastic tumours* includes those *arising from the lymphatic glands and blood-forming organs* generally. Amongst the former are the *lymphomata*, composed of tissue practically identical with the lymphoid nodules of a lymphatic gland, and which are of an innocent character. These have a malignant counterpart in the *lymphosarcomata*, which may be looked on as round-celled or mixed-celled sarcomata arising in lymphatic tissue. Both types of tumour may be difficult to distinguish from acute cases of Hodgkin's disease, which in all probability is in reality an infective condition. With regard to the other blood-forming organs, *myelomata* occur which spring from the multinucleate cells of the marrow, but many would look on the actual blood-forming cells of the marrow as the source of tumours, and consider leukæmia to be a tumour of the leucoblastic tissue, and polycythæmia to be a similar condition affecting the erythroblastic cells (see chapter on Blood).

Another disease which may be of a similar nature is the rare condition in the spleen in children characterized by a widespread proliferation of the endothelial lining of the splenic sinuses (*Gaucher's anæmia*), which may cause extreme enlargement of the organ and total filling up of the sinuses affected. The possibility of this being a tumour formation is indicated by the fact that in the lymphatic glands in the region of the pancreas in such cases a growth of endothelial cells has been observed.

**Tumours arising from the Hypoblast.**—The simple tumours arising from this embryonic layer present practically only one type, that of the *hypoblastic papilloma*, the structure of which has already been described. Of malignant tumours, the outstanding example is the so-called *malignant adenoma*, or cylindrical-celled cancer. This tumour is derivable from the columnar epithelium lining the intestine and the Lieberkühnian follicles. Its structure and varieties have also been described. As in other glandular malignant tumours, growths occur in the intestine in which a glandular plan is not evident, but which consist of solid masses of cells, thus presenting the feature of scirrhus or medullary cancer. In other words, we have here another example of anaplasia. In intestinal tumours in certain cases there is a tendency for a colloid degeneration, the result of which is the loss in the older parts of the tumour of all trace of cell formation. Sections here simply show large masses of colloid material embedded in a varying amount of stroma. When tumours undergoing this degeneration pierce through the intestinal wall, and infect the peritoneal coat, an excessively rapid growth frequently occurs, and the whole abdominal cavity may in the course of a few weeks be involved so that an enormous tumour results.

The *accessory organs of the alimentary tract are also the subject of tumour formation*—for instance, the *pancreas* and its ducts, the *bile-duct*, *gall-bladder*, and *liver*. The duct cancers are of a cylindrical

or scirrhus type, and occasionally in the gall-bladder there occur squamous-celled tumours to the genesis of which reference has been made. In connection with this metaplasia, it may again be pointed out that it is in this part of the intestinal tract that hypoblastic structures most nearly resemble simple epithelium, so that again, as in the case of endothelioma of the pleura, we have the association of similar structures arising from different embryonic layers, with the occurrence of similarity in the tumours derived from each.

Tumours also arise from the secreting structure of the pancreas, these being either simple adenomata or more frequently carcinomata, and special interest attaches to the primary tumours of the liver. Recent observations, especially on subacute yellow atrophy, have disclosed the fact that the cells of the liver possess a far greater capacity for multiplication than was formerly supposed. When any part of the organ is destroyed—as, for example, in the disease mentioned—active hypertrophy of the neighbouring liver cells occurs, and there is reason to suppose that the newly-formed tissue is functional. Even in ordinary cirrhosis, proliferation of liver cells and budding of new bile-ducts occur, and widespread hypertrophy is thus much in evidence. It has been shown that there is but a short step from such functional cell proliferations to the occurrence of adenomata of an innocent character, and also of malignant tumours. There is, in fact, evidence that in certain cases a tumour formation may follow on a simple hypertrophy. According to one view, the point of origin of both hypertrophy and tumour formation is especially the zone of junction between the liver cells and the ultimate bile-ducts. In simple adenomata the structure is that of acini lined by low cubical epithelium, and these neoplastic acini can sometimes be seen joining on to columns of liver cells. A similar acinous appearance is often manifest in the malignant tumours, but sometimes these manifest a more histioid character, and present appearances somewhat resembling those of liver cells.

**Congenital Tumours.**—There exists a very considerable group of tumours which are distinctly traceable to some congenital defect in development. These are very varied in character, and may roughly be attributed to two kinds of defects. The defect may consist in some simple error in development of a part of the body. An example of the simplest kind is the inclusion dermoid cyst, not infrequently occurring in the middle line of the chin. This is a cavity lined with skin, often producing hair, and often attached to the subjacent skin. It can easily be imagined that in the complicated infolding of the epiblast by which the mouth and nose are formed a small piece of extra epiblast has been included in a slightly aberrant site.

There are, however, tumours which are more complex in structure, in which several kinds of tissue—it may be derived from different

embryonic layers—are present. To account for these, three different possibilities arise, and, manifestly, discussion as to which explanation may apply in any particular instance must be largely of an academic nature. (*a*) In very early embryonic life cells may be accidentally cut off from their natural surroundings, may find themselves in unnatural surroundings, and may subsequently develop into tumours. (*b*) The process at work may be the same as that which accounts for the development of monochorial twins—*i.e.*, twins resulting from the complete division of one ovary. (*c*) Part or whole of one ovum may become included in another which develops into an apparently normal individual. It is important here to note that such developmental errors may not only involve the cells going to form the body of the individual (somatoblast), but also the cells which have a temporary nutritive function in forming the placenta (trophoblast). The whole subject of congenital tumours is intimately associated with the wider one of the occurrence of monsters.

The protean manifestations of congenital defect may be judged of by an inspection of the classification given on p. 234. The *first group* contains tumours arising from the junction of two embryos, or from a process analogous to the formation of monochorial twins —in either case from cells usually having the capacity of forming more than one embryonic layer. This group contains the grosser examples, of which the most frequent is the *teratoid dermoid cyst*. Here, attached to some external, often mesial, part of the body, or in internal parts, such as the mediastinum, or in some organ, notably the ovary and testicle, there are masses of growth in which are present representatives of all the bodily tissues, especially the skin, the central nervous system, bone, muscle, etc. There can be no doubt that these tumours are to be traced either to an early splitting of the embryo or to an inclusion of parts of one embryo in another. The teratoid dermoids are usually innocent, but malignant growths may arise in any of the elements of which they are composed. Specially interesting are the tumours occurring in the mediastinum, or about the reproductive organs in men and in virgin women, which are of the nature of *chorionepitheliomata*. These have the ordinary characters of similar tumours arising in women after a pregnancy—that is, they consist of blood-spaces lined by syncytial cells lying on tissue resembling the Langhans' layer of the placenta, and presenting great tendency to massive necrosis. They must be attributed to an inclusion of trophoblastic tissue during embryonic development. They are often part of a teratoid dermoid; they may remain quiescent till adult life, and then assume a malignant phase whose characteristics are indistinguishable from those of the ordinary chorionepithelioma.

The *second group* of congenital tumours comprises those arising in later embryonic life from the displacement of cells which usually are already so far differentiated as to be capable of forming only one

type of adult tissue. Here there may be greater difficulty in being confident that a congenital, and not a metaplastic, process is at work. Generally speaking, the soundest ground for assigning congenital defect as a cause exists when the tumour arises in some part of the body where at some stage of fœtal life the cells of one tissue must push aside those derived from another in order to attain their ultimate natural position. Any such alteration in relationship, or, what amounts to the same thing, any condition where the growth-rate of a tissue is for a time greater than that of its surroundings, furnishes an opportunity for displacement of cells; and there is evidence that in such cases, while in the cells embryonic activity may be temporarily diminished or may cease, the capacity for multiplication may be retained, and be again manifested after years have elapsed.

We may look at certain examples of this class of tumour. From the epiblast the simplest example is the *inclusion dermoid cysts* already described. Special epiblastic organs may also furnish examples of fault. Of these the suprarenal presents most difficulty. Tumours both innocent and malignant, stated to have the structure of this organ, have been described about the genito-urinary tract, especially in the kidney, and have been attributed to the misplacement of suprarenal cells during development (*suprarenal rests*). Recent work has, however, thrown some doubt on the possibility of recognizing with certainty suprarenal cells, or at any rate of differentiating between these and cells whose derivation from other, *e.g.* kidney, cells is traceable.

It is probable that tumours presenting the characters either of nerve cells or of nerve fibrils are of congenital origin. The nerve cell tumours recorded have been chiefly neighbouring on the brain or sympathetic ganglia in positions where normally nerve cells are not to be expected, and this, taken with the probability that nerve cells do not proliferate after fœtal life, points to the origin of *neurocytomata* from neuroblasts misplaced in the embryo. A similar explanation also probably holds good for the true *neuro-fibrillomata*.

Amongst mesoblastic tumours, many *osteomata and chondromata* occurring in young persons arise in the neighbourhood of epiphyseal junctions where irregularity in ossification can easily occur, as in fact it does in rickets. Certain chondromata unconnected with bone can also probably be traced to a congenital organ by portions of neighbouring cartilages being detached during development—*e.g.*, cartilaginous tumours in the parotid, which may come from the transformation of the primitive cartilage of the lower jaw. That the *striped muscle tumours* also arise from aberrant development is indicated by the fact that they are frequently associated with other congenital defects. In the case of some bone tumours arising apart from bone, it is difficult to form an opinion as to

origin. It has been shown within recent years that connective tissue in many situations in the body can undergo a metaplasia into bone under conditions of ordinary irritation, and thus it is possible that some tumours arising from connective tissue may likewise manifest a similar metaplasia.

Another group of tumours which are probably to be looked on as due to congenital defects are the *angeiomata*. These show variations in the details of their structure, but essentially consist of blood or lymph spaces (hæmangeioma, lymphangeioma) communicating with the neighbouring normal blood or lymph systems. They are chiefly found in the skin and the liver, but may occur in any part of the body. In the skin the hæmangeiomata constitute the "port-wine stains" and the cavernous nævi, the former consisting largely of dilated capillary-like spaces, and the latter of larger sinuses lined by flat or cubical epithelium. These sinuses are embedded in a greater or less amount of fibrous tissue, and between them there are often irregular blocks of cells resembling the lining cells, and which constitute evidence of vegetative capacity in the tumour. In the liver the blood-spaces are large, lined by flat cells, and are embedded in a firm fibrous matrix. The lymphangeiomata mostly resemble the capillary nævi in structure. The angeiomata as a class recall in structure the erectile tissues normally present in the body in the reproductive organs and in the nose, and represent a metaplasia of the circulatory apparatus of the body. That they are of congenital origin is evidenced by the fact that frequently they are present at birth, and also by their frequent association with the cutaneous mole which possesses a mixed cellular structure and is frequently hereditary. In fact, in the usage of continental pathologists the word "nævus," which in this country rather implies a hæmangeioma, is essentially applied to moles generally, of which the angeiomata are regarded as a special group. Sometimes a tidal character is recognizable in angeiomata, the greater portion of a tumour disappearing to reappear at a later date.

As stated, the *congenital cutaneous mole* shows variability in its histological structure, but usually it contains several elements derived from the superficial epithelium and its glands; these are ordinarily of rather imperfect character. In its interior there is often present a mass of pigmented cells. Opinion varies as to whether these are of epiblastic or mesoblastic origin. They not infrequently form the starting-point of malignant melanotic tumours.

Of congenital tumours generally it may be affirmed that sometimes their growth advances *pari passu* with that of the surrounding tissues; sometimes it is less, in which case the defects tend to disappear—*e.g.*, many angeiomata—and sometimes it is greater. This is especially true of the chondro-adenomata of the parotid and the ordinary cysts and dermoid cysts of the ovary. Usually speaking, the excess of growth is of an innocent character. In certain

cases, however, the growth tends to be malignant, and, again, certain parts of an ordinarily innocent congenital defect may assume a malignant type. Thus, epitheliomata may develop in dermoid cysts. It may also be observed that malignant epithelial tumours may occur where some simple congenital condition is present, as, for instance, in a persistent part of a branchial cleft in the neck.

**Parasitic Tumours.**—One small group of tumours has now been differentiated which are essentially parasitic in origin. These originate from the grafting of cells derived from an embryo on the maternal organism, in which they subsequently form true tumours, having sometimes innocent, sometimes malignant, characters. Differentiation of this group has followed upon the general recognition that the syncytia of the placenta and Langhans' cells are of fœtal origin. The *chorionic* or *hydatid moles* which sometimes occur during pregnancy in the uterus are derivatives of the elements of the chorionic villi. The mole essentially consists of a very complex dendriform structure composed of myxomatous tissue and Langhans' cells, covered with endothelium and syncytia in varying proportions, and it is to be looked upon as of the nature of a tumour derived from fœtal structures and nourished from the maternal organism. Usually it is innocent in character, and when removed or expelled from the uterus leaves no trace behind. Sometimes, subsequent to pregnancy, there appears in the uterine or cervical walls a tumour which presents a similar structure. The growing parts consist of irregular spaces containing blood, lined by syncytia which are placed upon cells resembling, or identical with, Langhans' cells of the placenta. This tumour was formerly known as a *deciduoma malignum*, but, since its pathology was elucidated, is now denominated a *chorionepithelioma*. It shows a tendency to local infiltration, and secondary tumours having a similar character are often found in the lungs, the liver, and the spleen. A special form of spread has been observed when such a tumour gains access to some of the large uterine veins. These may become plugged with the growth, which may extend up the inferior vena cava, and may even be found in the right chambers of the heart. In tumours of this kind necrosis is a marked feature, and there is sometimes evidence that, even when infiltration is widespread, retrogression and disappearance of the growth may occur. Both the chorionic moles and the chorionepitheliomata are due to the grafting of fœtal tissues on the maternal structure, and are therefore essentially parasitic.

### The Nutrition of Tumour Cells and their Degeneration.

If we put aside the angeiomata, which, as we have seen, are formed of elementary blood-spaces communicating with normal vessels, we may say that no tumour possesses anything more than a most

elementary blood-supply. We have seen that an advancing tumour stimulates the surrounding connective-tissue cells to divide, and this accounts for the presence of a fibrous stroma; and just as, in the formation of ordinary granulation tissue, there is not only a connective-tissue proliferation, but a budding out of simply-formed capillaries from the neighbouring capillary vessels, there is in tumour formation likewise a capillary development, and it is from these that the tumour is nourished. This formation, especially in certain innocent tumours, may be great in degree, and may result in the tumour being furnished with a very considerable quantity of blood. To keep up this blood-supply, the bloodvessels normally going to the part may undergo increase in size. Thus, in a simple ovarian tumour the ovarian arteries may become much larger than normal, and a similar phenomenon is often observable in malignant tumours. Generally speaking, however, the fact that no new arteries and veins are formed in connection with a tumour, and the fact of the great vegetative activity of the growing parts, lead to a tumour being insufficiently supplied with blood for the support of its older parts. Another factor contributing to the same effect is found in the growth of the tumour—either by direct infiltration or by pressure—leading to an occlusion of the neighbouring bloodvessels. Thus, frequently the life-history of tumour cells is short, and they often die. Great areas of necrosis, especially in the centre of a tumour mass, are thus common. These are indicated, naked eye, by the presence of greyish or yellowish patches, the microscopic picture corresponding to which is that of areas of amorphous débris, or of cells which either take on no stain or are slightly tinted by cytophilic dyes. Death of a tumour cell sometimes occurs without apparent previous degeneration, but frequently one or all of the ordinary cellular degenerations may be observed—*e.g.*, karyolysis, karyorrhexis, fatty, colloid, and mucoid degenerations. Where necrosis has been long-standing, calcification may be well marked, this being due to the deposit of lime salts from the lymph permeating the part. The best examples of such calcification are to be found in old fibro-myomata.

### Functional Capacities in Tumours.

Generally speaking, tumours take no part in the functions of the body. Thus, a person suffering from a fatty tumour may undergo great fat emaciation without the store of this substance present in the tumour becoming available for metabolism. In certain tumours, especially those related to the great organs of internal secretion, evidence of a functional tendency has, however, been noted. Thus, Hansemann (19) records the case of a malignant tumour of the thyroid the removal of which was followed by the occurrence of myxœdema. On a recurrence appearing, the myx-

œdematous condition became improved, to again reappear on removal of this secondary growth. Again, it is well known that tumours of the pituitary body are often associated with an overgrowth of bone, and in certain tumours of the suprarenal occurring in young children there has been a precocious development towards puberty, and an overgrowth of hair, the suprarenal gland being probably associated in some way with the nutrition and pigmentation of the skin.

Apart from these rare cases in which tumour cells play a part in normal metabolism, there is sometimes seen in neoplasms an attempt on the part of the cells to elaborate materials naturally formed in the tissues from which they spring. Thus, sebaceous secretion may occur in cysts in skin tumours; a fatty material resembling milk in the cells and ducts of breast tumours; and it is stated that bile has been observed in certain adenomata of the liver.

## The Etiology of Tumours.

The elucidation of the etiology of tumour formation constitutes one of the most important of the pathological problems of the present day, but it is well at the outset to recognize that as yet no definite conclusions have been reached on the subject. Notwithstanding the immense amount of consideration which has been devoted to the subject, only certain aspects have been investigated. Hitherto inquiries have been almost entirely confined to the factors operating in the causation of certain malignant tumours, especially those belonging to the cancer group. Even if the etiology of such growths were elucidated, it would still have to be proved that the same factors are at work in the causation of the simple growths. At the present time no complete scientific explanation can be given of the etiology of any tumour. At most, all that can be said is that in certain cases some of the proximate factors involved are more or less known; we are still entirely ignorant of the essential ultimate changes which are responsible for the perversion of normal reproductive tendencies in cells along the lines which lead to tumour formation. We can, thus, only discuss the parts which the proximate factors referred to play in the pathological processes involved.

1. **The Part played by Injury.**—Though there is a widespread popular belief that tumours are traceable to some definite injury, in the great majority of cases where this is assigned as a cause it is, to say the least, questionable whether an injury has played any part. There are certain cases, however, where a factor of this description must be recognized as contributing to tumour formation. The injury usually consists in the application to some part of the body of a long-continued series of slight irritations. If we put

aside the examples formerly given of such irritation, as, for example, the association of epithelioma of the lip with the smoking of clay pipes, or of epithelioma of the tongue traceable to injury of a jagged tooth, the occurrence of cancer of the scrotum in chimney-sweeps, we have at hand more striking examples of irritation leading to tumour formation. Thus, there are a considerable number of cases of epithelioma occurring in the hands and arms of those engaged in the refining of paraffin oil and of tar, and there is the striking case of the epitheliomata associated with exposure to the X rays. In all these instances we have as an outstanding feature the occurrence of malignant tumours in parts of the body which, in a general population, are rarely the seat of malignant disease. Further, in all we have the tumour formation preceded by an intractable dermatitis, often associated with hyperkeratosis, which presents the feature of not disappearing when the action of the irritant causing it is removed. There is thus in each case a tendency for a more or less permanent morbid effect to be produced on the vegetative capacities of the epithelial cells, and in certain individuals and in certain parts of the affected tissue this pathological tendency advances still farther, so that a tumour formation indistinguishable from that associated with less definable etiological factors takes place. In this connection it may be stated that such agents as the aniline compound Scharlach, and also certain oils, have been experimentally found to be capable of giving rise to aberrant proliferations of epithelium which, though not in themselves true tumour formations, yet histologically resemble epithelial growths. We must therefore recognize that epithelium is capable of responding in different ways to different irritants, and that, while injury by such a simple agent as heat stimulates a proliferation of cells which comes to an end when the breach caused by the irritation has been filled up,—with other irritants, a more permanent effect on the processes concerned in cell multiplication may be produced. Taking into account all the facts here known, we must admit that external irritants may, and in many cases actually do, constitute one factor—it may be the essential factor—in the case of especially epithelial tumours; and the possibility is thus opened up for many, if not all, of the superficial external and internal tumours of the body being accounted for.

The part played by injury in the etiology of tumours was early in the discussions on the subject recognized by Virchow, who looked upon the occurrence of a tumour as a special termination which might characterize certain inflammatory processes. At the time this view was put forward, however, the situation was complicated by the tendency to look upon what are still called the "infective granulomata" as representing processes intermediate between ordinary inflammations and tumour formations. Most of these granulomata have now assigned to them as etiological factors the

activities of definite infective agents—*e.g.*, the tubercle bacillus in tuberculosis—but the facts recorded above regarding the occurrence of malignant tumours in connection with chronic irritations open the pathway for Virchow's view being still held.

One aspect of the possibility of irritation leading to the genesis of a tumour is found in the view of many pathologists, that in certain cases what is known as a "precancerous stage" exists. The facts on which this view was formerly based were chiefly derived from a consideration of the so-called "Paget's disease of the nipple." In this condition a very chronic eczematous process occurring in the nipple is a frequent precursor of a breast tumour, originating in the largest ducts of the organ, and ultimately manifesting itself as an ordinary cancerous formation. The view taken was that a skin irritation was the starting-point of the tumour formation, histological facts being adduced pointing to the gradual transformation of inflammatory catarrhal processes in the epithelium of the ducts of the nipple into changes characteristic of new growth. In certain cases the occurrence of such histological developments preceding tumour growth appears to be substantiated. Thus, at the edge of certain epitheliomata of the tongue the papillæ of the epithelium seem, as the actual tumour site is approached, to show a greater and greater tendency to dip down into the subjacent parts until the region of the definite dendriform infiltration is reached. It is, however, difficult to say how far irritation of the parts about the tumour may lead to a general reaction of the epithelial cells corresponding to the similar process almost invariably met with in the surrounding connective tissues. It is certainly the case that in many epithelial tumours a sharp line of demarcation can be histologically recognized as existing between the normal and the cancerous parts, and it is thus probable that the existence of a precancerous stage in tumour formation does not occur in all cases.

2. **Intermittent Function.**—The fact that in the female sex by far the greater number of tumours causing death occur in either the breast or the uterus has drawn attention to the possibility of the intermittent function of these organs constituting a factor in the etiology of tumours. During the greater part of the life of the individual, and altogether apart from pregnancy, these organs are, in consequence of menstruation, the site of intermittent cellular activity, and it has been suggested that the periodic occurrence of waves of cellular multiplication opens up the possibility to a greater extent than in any other organ for the occurrence of aberrant cellular proliferation. It is certainly the case that the uterus is extraordinarily liable to tumour formation apart altogether from serious malignant tumours and of innocent fibro-myomata which give rise to symptoms. There are present in a very large proportion of women small myomata which, though causing no inconvenience,

nevertheless exist, and it is almost certain that in the intermittent function of the organs referred to we have a contributing factor towards tumour formation.

Periodic cellular activity may open up the path for slight injuries originating a perversion of vegetative capacity, and causing tumours to result.

3. **Heredity.**—There is a very common idea that a hereditary tendency may play a part in predisposing towards tumour formation. It is impossible at present to express an opinion on this subject. The occurrence of cancer is so widespread in the community that any individual suffering from the disease must almost necessarily show a history of tumour formation, it may be, in a near ancestor; but no data exist which show that, given a husband and wife both dying from cancer, a greater tendency exists in their children to develop tumours than obtains in the general community where the taint is less pronounced. The only tumours in which a hereditary element seems to exist are cutaneous moles, which are frequently found in the same parts of the body in parents and children. As a congenital disposition probably only accounts for a proportion of tumour formation, such an observation loses its significance.

4. **Trophic Nervous Influence.**—In certain cases the presence of a neurotrophic influence has been called in to account for the position of a tumour. Thus, rodent ulcers of the face sometimes in their course of spread seem to follow the distribution of a cutaneous nerve (7). The only tumour which the present writer has seen in which a neurotrophic element seemed to be present was in an individual with a capillary angeioma covering the whole of one half of the body except the areas of distribution of the ulnar and external popliteal nerves.

5. **The Doctrine of Embryonic Residues.**—This doctrine was originally advanced by Cohnheim to account for the genesis of all tumours, and it is still held by some to have such a general scope. Cohnheim (8) looked upon tumours as essentially due to congenital dispositions arising in embryonic life. The ultimate fact on which his views rested was the capacity which certain tissues possess of holding in reserve for many years a disposition congenitally implanted upon them. The examples he gives are firstly the reproductive organs, which remain histologically undeveloped till puberty, and secondly the uterus, with its capacity for thickening during pregnancy. Founding upon the persistence in the developing organism of such potential capacities for proliferation, he advanced the theory that during fœtal development small portions of tissue may be cut off from the site in which their normal development ought to occur, that these might be shut up for years in situations which they ought not to occupy, and at a

later period of life they might undergo a development unregulated by the laws which presumably determine the normal limits of growth of the tissue to which they originally belonged. As we have already indicated in speaking of congenital tumours, there is no doubt that such a misplacement of tissues can occur, the best examples being the infoldings of the superficial epithelium resulting in the formation of dermoid cysts. As will be presently seen, the occurrence of these, from Cohnheim's standpoint, is important, as their most frequent sites are in the skin of the face. The complicated infoldings which result in the formation of the nasal and buccal cavities in this region open up an easy path for errors of development occurring, gross examples being, of course, found in cleft palate and hare-lip. According to Cohnheim's view, if such an error can occur involving a gross sheet of tissue such as the whole thickness of the epithelium, the possibility is present for smaller errors occurring in which individual cells or blocks of cells could be similarly cut off.

Four chief sets of facts are advanced by Cohnheim in support of his view:

1. A very great proportion of tumours originate in positions where errors in development might easily occur, the great example of this being the occurrence of tumours about the orifices of the body—*e.g.*, growths about the lips, tongue, and bones of the face, the extreme developmental complexity of this region having already been noted. Other examples are found in the relative frequency of tumours of the œsophagus opposite the bifurcation of the trachea, this, as Cohnheim points out, being the situation in which the primitive respiratory tract arises from the primitive gullet. Again, uterine tumours are frequent in the cervix, and it is here that the ingrowing epithelium of the vulva meets the termination of the Müllerian duct; and in bone tumours a frequent site is the epiphyseal line, where the growths from different centres of ossification meet.

2. In support of his view, Cohnheim advanced the facts already alluded to relating to the frequency of tumours in organs where periodic cytological activity is most marked—*e.g.*, the breast and the uterus. From his standpoint, tumour formation here would not be so much correlated with periodic functional activity as with the fact that such activity would cause aberrant multiplication, not only in the normal cells of the part, but in cells which, during development of the organ, might have been cut off from their normal surroundings. As a side-point here, he stated that myomata of the uterus and adenomata of the breast are most common in unmarried women, and he put forward the consideration that when the stimulation to normal cellular activity is not present, the way is opened up for it proceeding along abnormal lines.

3. A third argument is based on the occurrence of hetero-

logous tumours; that is to say, of tumours composed of tissue not normally present in the organs from which they spring—*e.g.*, the cartilaginous tumours of the parotid and testicle, the striped muscle tumours of the kidney and heart, and the osseous tumours of the lung, which we have already referred to in dealing with congenital tumours.

From Cohnheim's point of view, the sites of these tumours present a constancy which suggests that the same developmental errors may periodically occur in certain parts of the body.

4. The atypical characters of the cells of tumours is also founded upon. Under normal conditions embryonic tissues may be looked upon as subject to laws under the operation of which the cells advance regularly to their final development. In rudiments cut off from the normal sites of their development, such laws would probably not operate, and atypical cellular developments might be expected.

There can be no doubt that developmental errors are responsible for the genesis of many neoplasms. Heterologous growths generally must be looked upon as having such an etiology, and it must be further granted that a developmental rudiment of a malignant tumour can exist for many years in an individual, and then assume the characters of a malignant tumour. Absolute proof of this is found in the tumours of the type of chorionepithelioma which have been recorded in the male sex, and which, as we have stated, are derived from inclusions of the trophoblast, either belonging to the individual or to an included ovum. In several such cases adult life has been reached before a malignant development of the residue has occurred.

Whether, however, Cohnheim's theory is applicable to the etiology of all tumours is more than doubtful. Looking at the sites of tumours, difficulties arise from our inability in many cases to trace or to admit the likelihood of developmental errors occurring. A definite example of this is found in the association of tumours with the occurrence of flexures in the intestinal tract. It would appear that the liability of these parts to irritation due to the changes occurring in the direction of the passage of the intestinal contents would suggest injury as a more likely cause of the liability to new growths; but the strongest facts militating against Cohnheim's view are those already given in connection with the occurrence of tumours in areas which have been subjected to irritation, and in which, under other circumstances, tumour formation is rare.

6. **The Parasitic Theory.**—There has from time to time been a tendency amongst pathologists to look to infection by a parasite for the origin of tumours. Proximate evidence of such a causal factor is strongest in the case of certain warts. Many dermatologists consider that this factor exists in the case of the ordinary multiple cutaneous papilloma, and even stronger evidence of

infection is found in the warts occurring in the course of gonorrhœal infections. Further, in the case of the dog, a condition histologically indistinguishable from sarcoma occurs, in which infection between male and female animals through coitus is undoubted. With regard to human malignant tumours, certain facts indirectly pointing to the existence of infectivity have been adduced. Amongst these is the prevalence of tumours in houses bordering on slow-running streams, and the existence of cancer houses—that is to say, of houses in which successive unrelated tenants have suffered from malignant disease. With reference to the latter, it is doubtful if a proper actuarial consideration of the evidence has ever been undertaken.

Within recent years, interest in the parasitic theory dates from the observations of Russell (9) in 1890, and of Ruffer and Walker (10) in 1893, on certain microscopic appearances in the cells of malignant tumours; and since the papers of these authors appeared, a great variety of organisms, mostly belonging to the protozoa or to the blastomycetes, have, chiefly on cytological evidence, been described in association with such tumours. Interest, however, mainly centres round the so-called *cancer bodies* as described by the authors named. The existence of these is undoubted, but controversy has turned upon the interpretation of the facts observed. The bodies are of very common occurrence in various groups of malignant tumours, but especially in those of an epithelial or glandular type. The numbers present in any particular case vary considerably, and in some instances they are present in a very considerable proportion of the cells. In sections stained by the Ehrlich-Biondi mixture, the smallest examples can be recognized in the cytoplasm of the cells as round, homogeneous bodies of a light, uniform, Cambridge-blue tint. The larger examples have the same general appearances, but sometimes manifest a central, round, reddish-stained body, embedded in a blue matrix, which sometimes tends to show slight radiate striation. The bodies are practically always circular, whatever their size, and may occupy the greater part of the cellular protoplasm, the nucleus being pushed to one side and folded round part of the cancer body. An enormous amount of work relating to these cytological appearances has been done, and the controversy has turned on whether the cancer bodies were to be looked upon as of a protozoal nature or as representing a special type of cellular degeneration. In the absence of the successful cultivation of any similar organisms from tumours in which they were present, the upholders of the protozoal theory have had to fall back upon evidence derived from analogies said to exist between the microscopic pictures seen in tumours and those presented in the infections of cells with admitted protozoal parasites, such as that of the biliary epithelium in the rabbit by gregarines.

At present the tendency of opinion is to regard the appearances seen as indicating a special type of cellular degeneration. The evidence for this view is derived from the work of Farmer, Moore and Walker. These observers showed that in bodily cells—*e.g.*, spermatogonia—where a reduction mitosis is a normal occurrence in cell life, appearances histologically identical with those seen in cells containing cancer bodies are present.

Apart from the discussions on the protozoal nature of cancer bodies, several observers, notably Sanfelice (20) and Plimmer (21), have isolated cultures of vegetable organisms belonging to the group of blastomycetes from tumour conditions in man and the lower animals. Experimental inoculation with such growths has re-resulted in reactions on the part of the bodily cells, which, however, usually are of a granulomatous character, and at present no evidence exists that a definite neoplasm has ever been originated in this way.

### The Infectivity of Malignant Growths.

Until recent years, as above indicated, the existence of an infective element in cancer was looked upon as extremely problematical. The occurrence of apparent cases of infection, as from husband to wife, was attributed to accidental coincidence, and set against such examples there was placed the fact that no case was recorded where surgeons had been infected through accidental wounds contracted while operating on cancer cases. The attention attracted by the putting forward of the parasitic theory, and by the statements regarding the occurrence of cancer houses, aroused, however, a new interest in the question; and although in this connection the word "infection" must be used in the general sense, which what we have to say will make apparent, it must be recognized that tumour formations can be transferred from one individual to another.

The starting-point of modern work lies in the observations of Jensen (11) on the possibility of communicating, through a series of animals, a tumour occurring in the mouse. Jensen described in the breast of such an animal a tumour of the type of an adeno-carcinoma, which resembled certain tumours occurring in the human female breast, but which differed in not giving rise to secondary growths. The growth continued until the mouse died of cachexia or from ulceration through the skin. In his original experiments, Jensen, by inoculating small pieces of the tumour, carried it through nineteen generations of white mice. From 40 to 50 per cent. of the inoculations practised were successful, and in various laboratories Jensen's original growth has, during the past years, been carried through an enormous number of generations.

Since Jensen first directed attention to the subject, the prevalence of tumours of this and other types (*e.g.*, sarcomata), especially in

mice, has been widely recognized, and many hundreds of such growths have been investigated in different parts of the world. It has been found that only in a certain proportion of cases has it been possible to transfer the growth from one individual to another, but when this has been done, the results have been similar to those obtained with Jensen's tumour. The primary importance of the results obtained lies in the fact that the conditions under which malignant tumours arise are now capable of experimental inquiry, and as this has progressed the close similarities existing between mouse tumours and growths normally arising in man have emerged. At first considerable doubt was entertained as to whether the adeno-carcinoma of the mouse was to be looked upon as a malignant tumour, and in many cases, both in primary and transplanted growths, no metastases were observed; but with the progress of knowledge many observations of the occasional occurrence of this malignant characteristic have been made (25). Emphasis must here be placed upon two points: Firstly, that for successful transference whole and uninjured cells of the growth must be used in transplantation. When the tumour material has been subjected to mechanical injury, growth does not result, and it is to be noted that the new tumour which is started originates from the proliferation of the infecting cells. The second important fact is that the successful transplantation of these tumours only occurs in animals of the same species as that in which the original growth was found, and that even different varieties of the same species show very different degrees of susceptibility, and in any case the transplantation is successful in only a certain proportion of the animals. The capacity for transplantation is not limited to tumours of the carcinomatous type, but has also been observed by Jensen in a sarcomatous tumour of the rat.

Attention may here be directed to a special instance of infection sometimes seen in human tumours—namely, the infection of an operation wound inflicted for the surgical removal of a tumour. If tumour cells detached from the main mass be scattered in the wound, they may settle down, proliferate, and originate fresh nodules of new growth. The danger of this occurrence is so well recognized that the surgeon, if possible, avoids actually cutting into a tumour during its removal.

Such being the fundamental facts observed, we may now consider some of the further results obtained. We have already noted the existence of insusceptibility in many individuals of a species, and this has been found to be probably due to some inherent capacity of resistance, and not to a failure in technique. This is evidenced by the fact that in the great majority of cases a second inoculation was similarly unsuccessful.

Another important fact which has emerged is that, when, as is frequently observed, the growth of a transplanted tumour comes

to an end, the animal, which has thus, as may be said, recovered from infection, now shows an insusceptibility to a fresh infection. In other words, a degree of immunity has been established, and, further, this immunity does not appear to be manifested only towards the tumour originally inoculated, but also towards other tumours. Thus, Ehrlich found that a previous inoculation with carcinoma material protected not only against all carcinomata, but also against sarcoma, and even against chondroma. Much work has been done with a view to elucidating the mechanism of this immunity, along lines similar to those observed in connection with immunity against bacterial infection. Whether, however, the processes are similar in the two types of infection has yet to be proved. Following such lines, some observers—Gaylord, Clowes, and Baeslak (12)—have found that the serum of mice which have spontaneously recovered from cancer transplantations confers an immunity upon other mice. In this connection, Ehrlich (13) looks upon two methods of immunity as possible—first, one depending upon the development of changes in the serum resulting in the formation of antibodies, such serum being capable of acting either actively or passively, and, second, a histogenous immunity, depending on the absence in the infected individual of receptors corresponding to those of the invading cells. As a variant of this latter mechanism, Ehrlich considers the possibility of the existence of what he calls an "atreptic" immunity, where the invading cells perish for lack of appropriate nutrition.

A fact of great significance has been observed in certain of the transplantation experiments. In these cases it has been noted that, in passing carcinomatous material through a series of mice, a sarcomatous development was observed which might ultimately constitute the only proliferative element present, this sarcoma being then capable of transference from one animal to another without the appearance in the tumours of any carcinomatous cells. The general view of this occurrence is that in some way the growth in the tissues of the carcinoma causes the connective-tissue reaction present in all tumour growths to become aberrant. We thus have an example of a new type of multiplication being developed in a tissue, which under ordinary circumstances does not occur in it. In passing, it may be said that the observations may throw light on what has been occasionally seen in man, where, in an individual suffering from carcinoma, a sarcomatous tumour, often in the neighbourhood of the primary growth, has occurred. Up till now the tendency has been to look upon such associations as accidental, but the results referred to open up the possibility of the second tumour being etiologically related to the first.

The chief bearing of the experimental work in animal cancer on the pathology of the disease as it occurs in man lies in the light which it throws on the possibility of a reaction taking place between

the tumour cells and those of the host, and especially on the possibility of the host successfully resisting the development of aberrant cell multiplication. Hitherto, where the spontaneous disappearance of malignant tumours in man has been stated to occur, the tendency has been to account for the facts by considering that a mistake in diagnosis has occurred; but it is now certain that such an explanation is insufficient, and a very considerable number of cases are on record where tumours have been shown, sometimes by repeated microscopic examination, to be malignant, and where recovery has undoubtedly taken place (22). Such facts, taken along with the immunization results in animals referred to, open up the way for the curability of cancer by treatment being attainable. It may be stated here as a possibility, that from time to time in man aberrations of cellular growth which are really tumours in embryo may occur, and that a mechanism may exist in the body by which the development of such aberrations is checked, and the gross tumours which come under the notice of the physician or surgeon may really represent cases where the reaction has been insufficient. That such an idea is not fantastic is indicated by the work of Teacher (14) on chorionepitheliomata, in which he demonstrated a process of natural healing as sometimes taking place in the primary and secondary deposits in this growth.

If we ask whether anything of really fundamental importance can be extracted from the very varied considerations we have put forward as to the etiology of tumours, our attention is directed to two main outstanding facts: 1. Certain tumours belonging to both the innocent and malignant groups are distinctly traceable to errors in embryonic development, the sequence being that, during the building up of the body, cells become detached from their normal positions, and, after being embedded for a longer or shorter period in their unnatural surroundings, take on a vegetative activity and assume the characters of a tumour. 2. In cells which have had a normal developmental history, and which for the normal purposes of the body maintain their capacity for division, these capacities may be modified in such a way as to produce new growths, which again may be either innocent or malignant. The sequence of events here is that by the long-continued application of stimuli, cell division is more frequent than would ordinarily occur; ultimately it comes to be outside the functional requirements of the tissue, and may be grossly perverted. We cannot, however, as yet say whether such an injury is the only factor at work in the production of the tumour, but we are justified in stating that it is an essential factor.

Whether a tumour arises from an embryonic residue or from the irritation of a normally-situated cell, it is important to note—and here it is well to confine attention to malignant tumours—that the

properties and capacities of the implicated cells are the same. In either case there is the capacity for great local proliferation, and there is the escape of living and potentially dividing cells into other parts of the body. Further, such capacities are not manifested by cells of any one bodily type, but are seen in the constituents of a tumour from whatever tissue it may be derived.

The conclusion to be drawn from such facts is that the change which produces a tumour affects characters shared by all types of cells, and which must be of a very primitive and fundamental nature. For many years attempts have been made to give a more particular expression to such a general statement, and to reach a clearer understanding of the changes essential to tumour processes, but these have produced little tangible result. The accumulation of facts pointing to injury as an essential factor in certain new growths has discredited the view that all tumours are due to a congenital disposition resident in the originating cell, and, on the other hand, the undoubted congenital origin of certain tumours and the similarity of the cellular aberrations in both cases would rather indicate that cells may be started upon a malignant path by more than one set of influences. Thus various theories have been advanced as to the conditions favouring the assumption of a neoplastic tendency by a cell, and as to whether any particular deviation from the normal path of cellular development marks a cell out for a neoplastic destiny. The possibility has been entertained of alterations in the normal physical relationships of cells being of moment, and the effect on this tissue tension of mechanical displacement, inflammation, etc., has been considered (23). On the other hand, the establishment of some fundamental change in the cell, such as that of which anaplasia is a visible sign, has been held to be sufficient without the occurrence of any further factor.

In none of these theories has the consideration of processes led to any clear conception of the underlying causal factors. Of these causal factors we are entirely ignorant, and we do not know whether, even if we exclude congenital tumours, there may not be a multiplicity of causes at work in different types of growth, nor are we likely to be in possession of any illuminating principles until something more is known of the laws which govern normal cell growth. It is probably only by a profound biological study of the conditions of cell life, especially in the lowest members of the animal kingdom, that advance in the understanding of neoplasms will come.

It is possible that in the future it will be necessary to direct attention to the effects which the chemical secretions of one bodily cell may have on the life-history of other cells. During recent years much evidence has been accumulated from the physiological side that one organ of the body can by its secretions influence the activity of another. Further, in the physiology of pregnancy,

not merely is the function of distant organs affected, but their cells may be stimulated to active division, the outstanding example being the cellular proliferation which occurs in the breast. Certain facts regarding tumours point to the possibility of factors of this type being at work. Thus, in certain cases the removal of the ovaries has been stated to cause the retrogression in tumours of the breast. During pregnancy, increase in the size of such tumours as capillary nævi may be observed, and we have the phenomenon observed by Ehrlich, of a breast tumour in the mouse giving rise to a sarcomatous development in the surrounding connective tissue. We must therefore admit the possibility of the chemical interdependence of cells being an important factor in the origin of neoplasms.

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# CHAPTER IX

# PATHOLOGY OF THE CIRCULATION

By A. E. BOYCOTT

**The Myocardium.***—"The cause of the heart-beat is too hard for man to conceive of"; it is only possible to express the observed facts in other words, and say that cardiac muscle exhibits the property of spontaneous rhythmical activity to a greater degree than do other excitable tissues. As far as the higher vertebrates are concerned, it is clear that this rhythmical contraction continues in the absence of any elements which can be regarded as definitely nervous in nature, and there is every reason to believe that the initiation and propagation, as well as the completion, of the actual contraction are purely muscular. This does not, however, exclude the possibility that there is, in the heart itself, a nervous mechanism which plays some part in the co-ordination of the contractions of the various muscles which compose the myocardium; in particular, some such mechanism seems desirable to secure that the commencement of one cardiac contraction shall not precede the termination of the preceding cycle.

The different parts of the heart are endowed with varying capacities for automatic rhythmical contraction. This power is most highly developed in the muscle about the termination of the great veins, where the rate of spontaneous contraction is greater than in other parts and where the cycle normally begins. The ventricular muscle can also, with some difficulty, initiate rhythmical contractions, but spontaneous contractions here occur at a slower rate than in the auricular muscle. The normal beat begins at the ends of the great veins in the mass of relatively undifferentiated muscle (sino-auricular node) situated at the junction of sinus and auricle, and the rate set by this muscle determines the rate of the whole heart. Experimentally the node is not indispensable, and it is also possible to make the cycle begin in the ventricle, and spread thence to the auricle. No clear case is known in human pathology in which this occurs, though there are reasons for thinking that the ventricle may

* See *Diseases of the Heart*, by James Mackenzie, 2nd ed., 1910, and *The Mechanism of the Heart-beat*, by T. Lewis, 1911, and the bibliographies given here.

interpose localized contractions in the due sequence of successive cycles. Even when the auricular muscle does not itself actually contract, it is difficult to be sure that it does not initiate the beat, and conduct it to a part of the myocardium which is capable of a mechanical response.

Abnormalities in the *initiation* of the beat may involve alterations in rate or alterations in rhythm. As a matter of practical inquiry, it is necessary to be careful that failure in conductivity from auricle to ventricle, or failure in contractility of the ventricle, are not mistaken for abnormalities of initiation. The rate of initiation must not be judged from the ventricular impulse or the peripheral pulse. The record of the jugular pulse and the electrocardiogram are the only criteria we have of the rate of initiation. These, too, may be imperfect, since auricular activity may be variable and at times imperceptible. Abnormal acceleration in the rate (*tachycardia*) is found in a variety of conditions. It occurs, for example, in many cases of cardiac disease, with a rise of body temperature, associated with exophthalmic goitre, in "paroxysmal tachycardia," from psychical influences such as fright. Abnormal slowing (*bradycardia*) occurs, *e.g.*, in some cases of cardiac disease, as a curiosity in otherwise normal individuals and as the result of the absorption of an excess of bile into the systemic circulation, as in jaundice. It is natural to suspect that these changes are brought about by various circumstances acting upon the initiatory muscle, either directly or through the nervous system. The increase of rate seen in fever is, within limits, proportional to the rise of temperature; the same increase is found when the temperature of the body is raised by simple means, such as checking evaporation from the skin, where the possible action of bacterial poisons is excluded, and is doubtless an example of the general biological law that when living substance becomes warmer it works quicker. Similarly, there seems little reason to doubt that bile acts directly. Emotional states and peripheral nervous impressions act either through the cardiac medullary centre or by producing sudden alterations in blood-pressure, a rise of pressure causing in general a slowing of the heart, a fall of pressure an acceleration. The slow pulse caused by a rise of intracranial pressure is in the same way associated with a considerable rise of arterial pressure. The alterations in rate found in cases of heart disease are to be looked upon as being mostly, but not exclusively, compensatory to the partial failure of the cardiac pump. The exact mechanism of this is not known. The correlation of the rate of the normal heart-beat with the amount of muscular work which is being done may be presumed to be brought about by the metabolic products in the circulating blood. Since any given heart is most efficient within a certain range of rate of beat, metabolic products, such as carbon dioxide, may cause either an acceleration or a slowing of the beat,

It is probable, therefore, that it is the accumulation of these metabolites, consequent upon a slowing of the general circulation, which causes a compensatory acceleration of beat in so many cases of cardiac disease. It is immaterial from this point of view how the pumping failure is caused ; it may be by gross disease of the valves, by the necessity of pumping at an arterial pressure beyond the powers of the available muscle, or by the impairment of the contractility of the individual muscle fibres by the action of bacterial or other poisons.

The rate of a heart which is somewhat imperfect may be normal while the subject is at rest ; any exertion, however, increases the rate much beyond the figure at which a normal heart would contract under the same circumstances. The acceleration of the rate of circulation which is required by an increase in metabolism is, in the healthy individual, secured partly by increasing the ventricular output at each beat, partly by increasing the number of beats. The diseased heart generally adopts the second method of adjustment more readily ; hence we may conclude that the natural margin of systolic output is being used to its maximum even at rest.

The influence of another factor must not, however, be overlooked. There is no doubt that intracardiac tension affords a powerful stimulus to contraction, and it may well be that alterations of mean pressure, and in the sequence of changes of pressure, in the auricles play some material part in bringing about changes of rate of beat.

The cause of the tachycardia associated with exophthalmic goitre is not ascertained ; the predominance of nervous phenomena in this disease suggests that it is of central origin. The real nature of " paroxysmal " tachycardia is quite unknown ; the heart beats at perhaps three times the normal rate in paroxysms of sudden onset and sudden cessation, each attack lasting from a few minutes to several days. It is associated with no ascertained structural change, and the cardiac cycle seems to be normally arranged.

In most instances of tachycardia, the acceleration is accomplished by shortening the duration of the diastolic pause. Systole, however, may also be shorter. In the case, for example, of the acceleration of rate which accompanies a rise of temperature, it is easy to see how the act of contraction should be faster, as well as the rate of initiation and conduction. With extreme degrees of tachycardia it is clear that systole must be shortened if the cardiac cycle is to escape falling into hopeless confusion. If normal systole occupies about 45 per cent. of the total time of a cycle, any increase of rate by more than about 120 per cent. will be impossible unless systole is shortened, or systole begins in the venous end before it has finished in the arterial end. With the heart beating as fast as 200 per minute, however, it does not appear that any such departure

from the normal order necessarily occurs. The explanation of how systole is easily accomplished more quickly than normal when the heart is beating very rapidly is probably to be found in the fact that at such rates there is not time for the heart to fill properly; hence the volume of blood to be expelled is less than normal. Furthermore, it is necessary to recognize that when any given heart exceeds a certain rate the diminution of intake, and hence of output, is such that it becomes a less efficient pump. This failure of pumping may be so marked as to produce a demonstrable fall in arterial pressure, and so make it still easier for the heart to perform its systolic work.

Alterations in the *rhythm of initiation* are not well understood. Irregularity of cardiac impulse or of radial pulse is common enough, both in hearts with gross structural disease or in the mildest cases of toxic arhythmia, such as may be produced by tobacco. In some cases these irregularities are due to abnormalities in conductivity, the auricle beating without being followed by the ventricle. In other examples, either the auricle or ventricle appears to contract on its own initiative, and without regard to the general rhythm of the beat. As far as the ventricle is concerned, the excitatory state which leads to these extra systoles may have originated in the ventricle itself, or in some part nearer the sinus venosus. In a large number of cases it appears that the auricle, usually as the final result of some gross cardiac lesion which has thrown extra work upon it, has abandoned a steady rhythm of effective contractions, and has fallen into a state akin to the "fibrillation" which may be often seen in the dying hearts of animals, or may be produced by ligature of coronary arteries. In this condition the auricles contract very rapidly, but arhythmically and quite ineffectively; their pumping action is probably nil; the ventricles respond occasionally and irregularly to this abnormal stimulation, or start an irregular rhythm of their own. Besides these groups of cases there are, however, occasions when the beat starts at the sinus venosus, and is thence propagated in the usual way, the irregularity being due entirely to an irregularity of initiation. The underlying causes are not known. Be it noted, however, that many of the most marked examples of irregularity occur in cases where the heart is failing to pump properly. The body as a whole is then deprived to some extent of its proper supply of oxygen, and, among the many derangements of function thereby produced, some imperfection in the rhythmical initiation of states of excitation and conduction in the heart itself is only to be expected. The effects of disease on the intracardiac co-ordinating nervous mechanism—if such exists—must also be considered, but of this nothing definite is known. It is difficult to see anything of a compensatory nature in these irregularities; extra systoles may perhaps be looked upon as of this nature.

Alterations in *conductivity* are of frequent occurrence. The clearest example is the failure of the auricular excitation to extend into the ventricles. The tissue which provides a direct continuity of muscular substance between auricle and ventricle is, in the higher mammals, of comparatively small bulk. Starting in the lower part of the wall of the right auricle, there is an isolated strand (*auriculo-ventricular bundle, bundle of His*) composed of muscular fibres showing little or no striation, and approximating to the embryonic type, which passes down behind the tricuspid valve through the lower part of the interauricular septum. It here divides into two main branches, which spread out under the endocardium over the ventricular walls and finally end in the columnæ carneæ. At the upper end of the bundle is a mass of similar undifferentiated muscle (auriculo-ventricular node); this has no direct connection with the sino-auricular node. No other muscular connection between auricle and ventricle exists, and there is clear evidence, both experimental and clinical, that division of the auriculo-ventricular bundle may prevent the auricular excitation spreading to the ventricle. If the bundle is actually cut across, the ventricle comes to a standstill unless and until it begins to originate beats for itself and at its own slow rate. Graduated compression of the bundle gives rise to states in which every second or third or fourth auricular beat forces the partial block and excites a ventricular contraction. In other cases, though the impulse gets through, the rate of propagation is diminished and the ventricular contraction delayed. The more extreme examples of "heart-block" which occur in man produce the symptoms of Stokes-Adams disease. In this condition the ventricular rate becomes so slow that the supply of blood to the brain fails, and unconsciousness follows. Examination of the auricular contractions through the impulses in the jugular vein shows that this is not a bradycardia due to slow initiation, but a failure of conduction. While the auricle beats, *e.g.*, seventy-two times per minute the ventricle shows only thirty-six or twenty-four contractions. The numerical correspondence, which indicates that the block is only partial, and that every other or every third auricular beat extends to the ventricle, is commonly sufficiently exact to make it improbable that in these cases in man we have to deal with the establishment of an entirely independent rhythm by the ventricles, such as may be readily produced in the lower animals by compression of the muscular fibres between auricle and ventricle. It appears to take the ventricle some time to begin automatic contraction after it has ceased to receive impulses from the auricle, and it is hardly likely that in man this interval could often occur without general death, though in rare cases it seems clear that the rhythms of the auricle and ventricle have become completely independent. In some cases, as the ventricular rate diminishes the auricular rate increases—a curious

phenomenon which is perhaps due to over-stimulation of the auricle by increasing internal pressure arising from the obstruction in front provided by the passive ventricle. In many examples of Stokes-Adams disease, definite disease of the auriculo-ventricular bundle has been actually observed. Most commonly the fibres are more or less destroyed by involvement in an area of syphilitic inflammation, but new growths and other changes may lead to the same result. It would be unreasonable to suppose that we should be able to detect structural alterations in all cases of functional derangement, or to estimate quantitatively the degree of functional failure that must be associated with a given amount of anatomical change. Cases, therefore, where heart-block had occurred without obvious change in the bundle of His, or where the changes found have seemed to be either too little or too great to account for the condition observed during life, must not be taken as necessarily disproving the main conclusion that Stokes-Adams disease is due to impairment of conductivity through the auriculo-ventricular bundle. In the course of the severe general illness produced by various infections, notably in diphtheria, dissociation of the auricle and ventricle also occurs ; this may be only temporary, disappearing with convalescence. In some of these cases localized foci of acute inflammatory change have been found in the auriculo-ventricular bundle ; in others the condition is doubtless due to the functional impairment of the muscle of the bundle by the poisonous action of bacterial products.

Heart-block of mild degree, insufficient to cause the very obvious general symptoms of Stokes-Adams disease, is not infrequent. In this category we include also cases where, though every auricular is followed by a ventricular beat, some auricular excitations are so nearly blocked that the corresponding contraction of the ventricle is reduced to an ineffective flick. Many cases of " tobacco heart " are of this kind, and the condition is not uncommon in hearts with gross disease. The latter examples are probably due to impaired circulation through the bundle of His itself, the blood-supply of which is mostly distinct from that of the ordinary muscular tissue surrounding it.

It is obviously difficult to have any precise knowledge of abnormalities of conduction between individual fibres or small areas of heart muscle. There is, however, one important and common disease in which it seems that something of the kind must occur. In the condition known as " *fibrous heart* "* or " chronic interstitial myocarditis," irregular masses of muscle fibres have been destroyed, most commonly in the apical third of the left ventricle, and replaced by an overgrowth of the neighbouring connective tissue. Some muscle fibres are entirely isolated. What these do cannot be ascertained, but if they contract at all it is difficult to see how they

* Cowan, *Journ. of Path.*, 1904, vol. ix., p. 209.

can do so in their proper sequence. Other fibres are partly isolated in such a way that it seems clear that the excitatory state must reach them by an abnormal route. For the proper performance of ventricular systole it is necessary that the impulse should reach the different muscular masses in the right order and just at the right time; and the destruction of muscle fibres is of importance, not only because of the loss of contractile substance, but because the normal path of conduction to other fibres may be destroyed. Besides the "fibrous heart," this localized loss of substance is chiefly found in infarcts and syphilitic granulomata.

In considering the abnormalities of *contractility* of the heart, it is always of prime importance to consider the contractility in relation to the amount of work which has to be done. The contractile power of a normal heart is inadequate if the volume of blood to be pumped, and the pressure to which it has to be pumped, are extraordinarily increased; while a heart with a much damaged musculature may be a reasonably effective organ if the work in front of it is appropriately reduced. In estimating the contractile power of the heart, it is important, especially when, as in human disease, there may have been ample time for compensatory adjustment, not to take the arterial blood-pressure as the sole index of efficiency. The object of the heart is to pump 3 or 4 litres of blood round the body every minute; it may entirely fail in this without there being any fall of arterial pressure, which depends as much on peripheral vaso-constriction as on the output of the left ventricle. We have not, unfortunately, any satisfactory method whereby the rate of circulation in man can be properly determined; and unless the failure of contractility is so great as to give rise to obvious general symptoms of failure of the circulation, we cannot really say whether the heart is working effectively. We have therefore to judge of contractility by such criteria as the force of the apex beat and of the peripheral pulse, which naturally cannot be expressed quantitatively. The chief conditions which must be associated with diminution of contractility may be conveniently noted here, premising that the excitability, conductivity and other functions of the cardiac muscle will probably be more or less affected simultaneously. The contractile power of the musculature, taken as a whole, will obviously be diminished if there be destruction of muscular substance without compensating regeneration. We are, however, more concerned here with conditions which impair the functional capacity of the muscle fibres individually without necessarily leading to their anatomical obliteration. The rare condition known as *fragmentation*, in which the fibres are found broken across, leads to such a loss of contractility as is incompatible with life. The same is true of complete or nearly complete deprivation of oxygen, as in asphyxia, and of many poisons of different kinds. Of harmful influences which are not so completely destructive, the most impor-

tant are—(1) impaired nutrition, often arising from an imperfect circulation primarily due to the failure of the cardiac pump itself; (2) bacterial poisons, whose action may be rendered more effective by the coincidence of the fever which they also cause. Good examples of these are found in the toxins produced by the pneumococcus, the diphtheria bacillus and the plague bacillus, which have a profound direct poisonous effect on the vitality of cardiac muscle, which is often the actual cause of death. Many other infective agents have the same action to a greater or less degree; among these the *Micrococcus rheumaticus** occupies a special place. In addition to its action in producing inflammations of the pericardium and endocardium, and in this way being one of the chief causes of gross cardiac disease, it poisons the myocardium, giving rise to serious inefficiency, and also produces obvious structural alterations in the interstitial connective tissue. Even if the muscle fibres were themselves functionally intact, their contraction would apparently be mechanically impeded by the inflammatory exudate and growth of fibrous tissue which are the patent anatomical expression of the myocarditis. Bacterial toxins may, as in the case of acute rheumatism, cause actual destruction of a few muscle fibres. Generally, however, the anatomical change is not very great, some degree of "cloudy swelling" and fatty change† alone being found. The presence of droplets which give the reactions of fat within the muscle fibres is due to a definite cytoplasmic disintegration whereby the fat, which in the healthy cell is combined with protein, is set free and becomes manifest as free fat. The degree of fatty change brought about by bacterial poisons varies very much in different cases. It is particularly well marked in the case of diphtheria infection. More exaggerated degrees of the same condition are produced by phosphorus and some other inorganic poisons, and may also be caused by general or local deficiency of oxygen.

In the lower animals *tonicity* of the heart muscle may be easily demonstrated. It appears to be a function of the sarcoplasm rather than of the fibrillar substance. Actual experimental proof of a similar condition in the mammalian heart is not so easy to obtain, and the action of the pericardium in preventing over-distension of the heart renders it desirable to be cautious in the interpretation of experiments in which the pericardium is opened. There is not sufficient direct evidence to show that the heart muscle is in a continual state of tonic contraction, upon which the ordinary beats are superimposed, in the same sense as are the voluntary muscles of the normal active subject. But some such assumption seems necessary to explain how it is that in some hearts the muscle seems to give way rather easily, and so allow the chambers to become unduly dilated, and there are fairly good reasons for thinking that

* Beaton and Walker, *Brit. Med. Journ.*, 1903, vol. i, p. 237.

† Cowan, *Journ. of Path.*, 1903, vol. viii., p. 177.

in many diseased hearts the onset of definite pumping failure is accompanied by a flabby and atonic state of the muscle.

**The Nutrition of Cardiac Muscle.**—The proper nutrition of the cardiac muscle is a cardinal factor in the maintenance of the circulation as well as in the resistance of the heart to circumstances which are detrimental to its efficiency. The importance which the economy attaches to the adequate nourishment of the heart is well illustrated by the fact that after prolonged starvation the substance of the heart is diminished by only about one-tenth of the wasting found in the skeletal muscles.

The heart requires the same sort of food that is wanted by the other organs, but it differs from many of these in that the supply must be fairly steady and continuous. Though the heart can diminish the work it does, it cannot tide over a period of failure of food-supply by taking anything like a complete rest. As with the secreting cells of the kidney, some cells of the central nervous system, etc., cardiac muscle can only withstand a very brief period of oxygen starvation without dying. A shortage of other forms of food may be made up by drawing on the amounts stored elsewhere; there is no such store of oxygen in the body. It is therefore important as well as convenient to think of the oxygen-supply as being the chief item in the nutrition of the heart.

The supply of oxygen may fail from general causes which affect the heart in common with the rest of the body, such as asphyxia, severe anæmia, carbon monoxide poisoning, etc., or it may be locally defective in the heart alone, as in blocking of the coronary vessels. If the blood is deficient in oxygen-carrying power, the heart may yet obtain a full supply if, by adjustment of the coronary circulation, more blood can be passed through the muscle in unit time.

The quantity of blood available at any time for the use of the myocardium is regulated by many factors. A certain amount of blood can find its way from the chambers of the heart into the coronary circulation, for by means of the veins of Thebesius all four cavities are linked with the coronary veins. Experimentally it has been found possible to maintain an active beat of the excised mammalian heart fed only from the right heart. It is, however, clear that this circulation is of subsidiary, and probably of minimal, importance. Ligature of one coronary artery in the dog is, as a rule, quickly followed by the permanent arrest of the heart. Occlusion by an embolus in man is not an uncommon cause of sudden death. To produce this effect, it is not necessary that the whole blood-supply of the heart should be cut off. Blocking of one main artery, or even a single large branch, generally produces so much disorganization of the musculature that the whole heart is brought to a standstill. On the other hand, the occurrence of old infarcts shows that local anæmia sufficiently severe to cause death of a notable mass of muscle is not necessarily incompatible

with continued and efficient cardiac action. If the obstruction of the vessel is only partial, or reaches the stage of complete occlusion only slowly, a collateral circulation from the other arteries and from the Thebesian vessels can to some extent be established. In this way the normal arterial supply can be largely obliterated without an immediately fatal result. As a matter of fact, arterial disease, which is the common cause of a progressive diminution of the calibre of the coronary arteries, is generally pretty evenly distributed among all the vessels. The opportunities for establishing a good collateral circulation are therefore small, and the muscle, beside being, no doubt, functionally impaired, undergoes degenerative changes. Muscle fibres die and are replaced by fibrous tissue. The effect of this fibrosis on contractility and co-ordination have been already mentioned. Note, however, that the heart wall, though tougher to the touch, loses elasticity, becomes less able to withstand a variable strain, and is more liable to actual rupture. A moderate degree of coronary arterio-sclerosis, producing no obvious diminution of lumen, may also be of importance in that it reduces the capacity of vasomotor response, both in varying states of more or less normal functional activity and in conditions of disease which might be compensated by the vasomotor apparatus.

The volume of blood passing through the coronary circulation has an immediate and marked influence on the force of the heart-beat, though, within limits, it may have little effect upon the rate. The force of the heart-beat is also an important factor in determining the volume of the coronary flow. Any circumstance which diminishes the efficiency of the cardiac contractions is found experimentally to diminish the flow of blood through the myocardium. At each systole the blood is squeezed backwards towards the aorta, and onwards towards the coronary veins, and the refilling of the coronary circulation is dependent upon the aortic pressure and the diastolic interval. An imperfect systole therefore would mean a poor coronary circulation, especially when, as in many cases in human pathology, the rate of the heart-beat is much increased. The difficulties introduced by irregular co-ordination of the systole of different parts of the heart are obvious. In many examples of cardiac disease the bulk of muscle is also much increased, and it is a fair presumption that, if there is twice as much muscle, twice as much blood will be wanted for its proper nourishment. If the chambers dilate and the wall becomes stretched, a further impediment to the easy entry of arterial blood arises, while the increase of intra-auricular pressure which is often present helps to prevent the proper escape of venous blood. There are thus a variety of local reasons why a heart which is inefficient should receive less nourishment just when it wants at least its normal amount. In the ramifications of this vicious circle, some attempt at compensation should be discoverable. It may perhaps be found in a local

vaso-dilation in the heart. It is somewhat singular that with a very ineffective heart the arterial pressure is usually kept up to the normal level, or even higher. The rate of the circulation must be much diminished, and so the body as a whole is to a greater or less degree short of oxygen. But the high arterial pressure with local vaso-dilation might give a good supply of blood to a relatively small vascular area, such as the myocardium. And in this connection it is worth noting that the coronary vasomotor apparatus differs in some important particulars—*e.g.*, the response to adrenalin—from that elsewhere.

**Alterations in the Quantity of Cardiac Muscle: Hypertrophy.**—Defects of general nutrition have only a small effect on the bulk of cardiac muscle, and their influence on the functions of the heart are relatively inconspicuous among the more obvious sufferings of other organs. The heart is, however, liable to be smaller than usual in cases of long-standing disease, such as phthisis, and in those who have reached old age without meeting one of the many causes of cardiac hypertrophy. In both cases two factors are probably at work: defective nutrition, and a quiet life with no call for a vigorous circulation. The muscle fibres are smaller, and the perinuclear pigment is more concentrated; hence the condition of "brown atrophy." It appears that the loss of functional capacity in such hearts is commonly less, relatively to the total capacity of the heart, than the normal reserve, so that it is only at times of unusual stress that it becomes manifest.

An increase in the amount of heart muscle is a very common condition. Whether this hypertrophy depends on an increase in the number or size of the individual fibres is not, and from the nature of the case probably never will be, fully determined. There are strong grounds for believing that an actual increase in number (hyperplasia) may take place. At the same time it is clear that the great proportion of the increase in total bulk is due to enlargement of the fibres (hypertrophy *sensu restricto*). How far hypertrophy may be directly caused by excessive intake of food is very doubtful. It would be an irrational process, and it seems probable that the enlarged heart which has been associated with "high living" is compensatory to some of the ills due to the gluttony and alcoholism associated with that mode of life. Regarding, then, hypertrophy as a definite purposive process, arising in response to a definite stimulus and directed towards a definite end, we find that the common, and apparently the only, cause of cardiac hypertrophy is increased circulatory work. A measure of the magnitude of the stimulus to hypertrophy is given by the difference between the amount of work which any given quantity of heart muscle is called upon to do, and the amount which is appropriate—*i.e.*, which has the same relation to the size of the heart as the normal amount of cardiac work has to the normal weight of the heart.

The heart may have more work to do from a great variety of causes. In the first place, the pump itself may be imperfect. Thus, if in systole the mitral valves leak, and some of the blood which should go into the aorta returns to the left auricle, the left ventricle must, if the proper quantity is to pass into the aorta, expel in all more than the normal amount of blood, and, if the aortic pressure is maintained, must do more work. In the same way it is harder work for the right ventricle to pass the proper quantity of blood into the lungs through a pulmonary orifice ½ inch in diameter than through a normal-sized aperture. If the two layers of pericardium are adherent to one another, the heart can no longer wriggle as it would, and is at an obvious mechanical disadvantage. In all these and in other similar conditions, the hypertrophy of the heart is a direct compensatory attempt to pump the proper amount of blood round the body in a given time, and it therefore involves that part of the heart on which extra work is thrown—the left ventricle, the right ventricle, the whole heart, as the case may be. It is, however, in fact uncommon to find hypertrophy limited to one chamber of the heart. The right ventricle normally has just about half as much muscle as the left. With stenosis of the pulmonary orifice it becomes much bigger, and in so doing must necessarily disturb the due relationships of the different parts of the heart to one another, and of the heart as a whole to the thorax and its contents. As a result the left ventricle is somewhat embarrassed by the excessive size of the right ventricle, and consequently also hypertrophies. Persistent increase in rate of beat is liable to cause hypertrophy, as, for instance, in exophthalmic goitre. Any enlargement of the cavities of the heart necessarily affords a stimulus to the growth of the muscular walls, since these have more blood to deal with and therefore more work to do.

In the second place, the origin of the extra cardiac work may lie outside the heart. It may be necessary to expel the normal amount of blood against an abnormally high aortic pressure. The causes of the persistent elevation of arterial pressure which is so common in adult life are dealt with elsewhere (p. 311). A pressure of about 180 millimetres Hg, which is often reached, increases the work of the heart by some 50 per cent. As a matter of post-mortem experience, this is undoubtedly the most frequent cause of any form of cardiac hypertrophy, the left ventricle naturally being chiefly affected. If the rise of pressure is in the pulmonary artery instead of the aorta, the right ventricle is involved. Such a condition is found in emphysema, where the air cells are distended, and frequent fits of coughing raise the intrapulmonary pressure, and so compress the capillaries. On the other hand, the aortic pressure may be normal, but the volume of blood to be pumped may be excessive. If the concentration of hæmoglobin in the blood is diminished,

the correct amount of oxygen can be supplied to the body only if the quantity of blood circulated is increased. In chlorosis, for example, there are reasons for concluding that this actually happens (p. 22), and, though the absence of fatalities precludes accurate observation, there is no doubt that in many cases the heart is enlarged. The same factor is probably also chiefly responsible for the hypertrophy associated with hard physical work. Here the greater metabolism requires a more active circulation. There are also at least two other contributory factors in these cases, especially when, as in athletes, the muscular work is of an excessively severe degree, but of relatively short duration. Muscular activity of this kind involves a considerable rise of blood-pressure, and in many instances the thorax is fixed with a closed glottis and the circulation obstructed by an increase of intrathoracic pressure. In this connection it is worth noting that the rise of arterial pressure need not last long to cause hypertrophy of the left ventricle. Repetition of the considerable though very transitory rise produced by adrenalin* brings about a considerable hypertrophy experimentally. An increase in the viscosity of the blood, as in polycythæmia (p. 19), may be associated with a notable degree of hypertrophy. The conditions are, however, complex, and it should be noted that, owing to the increase in hæmoglobin concentration, it is not necessary that the circulation should, as far as the oxygen-supply is concerned, proceed as fast as normally.

Such are the common causes which provide the stimulus which may bring about cardiac hypertrophy. Whether the response is normal depends on several factors. In the first place, the excess of work thrown on the heart must not be too great in relation to the time of its development. The normal heart may altogether fail to cope with a moderate quantity of extra work of very sudden onset, whereas if the increase of work is presented to it bit by bit it may be able to deal satisfactorily with an amount almost enormously in excess of the normal. Thus, the rupture of one segment of the aortic valve of a healthy heart by external violence is a proposition which commonly overwhelms the left ventricle, and death ensues before any material hypertrophy occurs. A far greater absolute degree of valvular destruction and incompetence, arising by the slow progress of disease spread over several years, may result in such a degree of hypertrophy as is fully compensatory. The time relations are therefore of great importance. It is clear that the extra work arising at any moment must be less than the greatest amount with which the muscle existing at that time could possibly deal. If the strain put on the heart is such that the efficiency of the pumping is impaired, the possibilities of adequate

* Adrenalin also produces myocardial fibrosis, and this may contribute to the cardiac hypertrophy. In man fibrous hearts are commonly above the normal size.

hypertrophy may be forthwith diminished by the partial failure of the coronary circulation. For it is obvious that, if the heart muscle is to grow, it must have a proper supply of food. Hypertrophy, therefore, is liable to fail where the general nutrition is imperfect or where local conditions starve the heart. Of the latter, a loss of elasticity and narrowing of the coronary arteries is especially important, in that the same condition in the vessels of the body generally leads to an enduring rise of arterial pressure, which affords a common stimulus to hypertrophy. The capacity of growth is markedly diminished in the aged, and one sees curious variations in the degree of response in different persons under apparently very similar conditions. The same thing is well known in reference to the work hypertrophy of skeletal muscle. Lastly, it is pretty obvious that muscle fibres which are diseased or under the influence of toxic agents will not hypertrophy as well as normal tissue.

If, then, the stimulus is appropriate—and suitability here seems to be mostly a question of being small enough—and the muscle be in a healthy state, hypertrophy of the heart will take place. And this hypertrophy will be adjusted quantitatively to the stimulus, so that the enlarged heart is able to do with ease the abnormal amount of work which is required. If no further increase in work is presented to such a heart, the circulation may be kept going in a proper manner almost indefinitely. Examples of such a condition are found in some cases of congenital abnormality of the heart (*e.g.*, narrowing of the pulmonary orifice). But in the great majority of cases of cardiac hypertrophy in man the stimulus is being constantly repeated. In valvular disease, for example, the narrowing of the orifice or the incompetence of the valves is continually and progressively increasing, and by the time the heart has become big enough to deal with the obstacle in its original form the difficulty has become greater. In the same way the vascular changes, which lead to a narrowing and a loss of elasticity of the arteries and an increase in blood-pressure, as a rule steadily progress. Though the growth of the heart may for a long time keep step with the increasing amount of work, a time eventually comes when the hypertrophy will no longer be adequate. Everybody who has a hypertrophied heart will certainly not die of heart failure; but, allowing for those who die, as it were, prematurely from other causes, it seems that these large hearts, with few exceptions, must inevitably come to a bad end. The most obvious reason why this should be so is, simply, that there is only a limited amount of room within the thorax. When the heart surpasses a certain size, it must be uncomfortably situated with regard to the spine, sternum, and ribs. The restrictions imposed by its bony surroundings increase its difficulty in doing the increasing amount of work; in other words, the very fact that the heart hypertrophies brings it still more extra work to do. The absolute amount of hypertrophy

which is possible is thus rather strictly limited; if the stimulus subsisting requires more than this, the circulation must fail. A large heart also requires more food, and, unless the coronary circulation is in good order, difficulties will ultimately arise from this source. When there is definite pumping failure, the nutrition of the heart may be seriously affected both by a diminution of the coronary flow and by the general upset of the alimentary canal which is so common under these circumstances. This is perhaps the real explanation of the fact that the downhill progress of hypertrophied hearts is, once it begins, often very rapid. Other subsidiary factors may perhaps be found in the disturbance of respiration by the abnormal size of the heart, and in the increased viscosity of the blood which is sometimes present, but it does not seem likely that these can be of much importance. It should, however, be understood that the ultimate failure of hypertrophied hearts does not take place in accordance with an axiomatic law that all hypertrophied muscles fail in the end; there are no grounds for supposing that such a law is true.

**Enlargement of the Cavities of the Heart: Dilatation.**—An increase in capacity of one or more of the chambers of the heart may occur either as an adaptive mechanism to increase the output, or as a calamity which overtakes the myocardium against its will.

A good example of the former condition is seen in cases where the aortic valves are so diseased as to be incompetent during diastole. After the left ventricle has ejected its normal 100 c.c.* into the aorta, during diastole some 30 c.c., for example, of the blood regurgitates from the aorta, leaving only 70 c.c. to go on round the body. The obvious way out of this difficulty is to enlarge the cavity of the left ventricle, and increase the systolic output to about 130 c.c., so that, allowing for the amount returning to the ventricle during diastole, the body at large will get the proper amount at each heart-beat. Similar conditions obtain if the mitral valve is incompetent during systole to a similar amount. The right quantity of blood can, again, only be put effectively into the aorta if the actual volume contained in, and then discharged from, the ventricle is greater than normal by the amount which goes back into the left auricle. In both cases compensation for the defect is attained by increasing both the bulk of muscle and the capacity of the chamber. We may well suppose, though here our knowledge of what actually happens is not so complete, that a general adaptive increase in capacity occurs when the volume of blood to be sent

* This figure is taken for illustration only. The ordinary systolic output in man is not known, but it is pretty certain that it is somewhere between 50 and 100 c.c. All the blood in the body (3½ litres), probably, during rest goes through the heart about once a minute, giving an output of about 50 c.c. Calculations from observations on animals suggest a figure of about 85 c.c.

through the heart per minute is much increased, as in habitual hard muscular work or in chlorosis.

On the other hand, a chamber may be forcibly distended and dilated by blood being passed into it at a higher pressure than the muscle of the walls can withstand. This naturally occurs most easily with the thin-walled auricles. If the auriculo-ventricular valves, and especially the mitral valve, be incompetent during ventricular systole, the auricles receive a certain amount of blood at the intraventricular systolic pressure. If the leak is a large one, there may be time for the intra-auricular pressure to be increased far beyond its normal level, and that, be it noted, at a time when the cavity is at its largest, and the walls least able to resist forcible distension. How small an increase of pressure is necessary to dilate the auricles may be demonstrated by animal experiments. By injecting fluid too quickly and at too high a pressure into the jugular vein, it is surprisingly easy to blow out the right auricle, and thus bring the whole heart to a standstill. Whether the ventricles are ever forcibly dilated in a similar way is doubtful. Unlike the auricles, blood cannot enter them at a pressure above that which, during systole, they are accustomed to stand. It is true that in aortic regurgitation, for example, the return flow of blood from the aorta enters the ventricle when it is not in active contraction; but it is very doubtful whether this takes any part in causing the increase of capacity which occurs in these cases.

But there is no doubt that the capacity of the ventricles may be much increased by processes which are detrimental rather than compensatory. The typically ineffective ventricle is dilated, with a flabby wall, which seems hardly likely to be able to expel its contents to very good purpose. Such a condition is seen in its simplest form in hearts poisoned by the toxins of diphtheria, rheumatism, plague and other bacteria. It also occurs as a final stage in hearts which have had too much extra work to do, either because of some sudden and excessive increase (as in a ruptured valve), or from the ultimate failure of hypertrophy to keep step with a slowly-progressing difficulty (as in valvular or arterial disease). Both of these main groups of causes may be combined, as when a heart already doing extra work is further weakened by acute poisoning, a combination not infrequent in repeated attacks of acute rheumatism. Though the ventricle may burst itself by the violence of its own contractions, the actual rupture takes place in an abnormal area where the muscle has, usually, been replaced by fibrous tissue. And it is hardly conceivable that the force which distends the ventricular wall is the intraventricular pressure which has been created by the contraction of that same muscle. The essential change underlying these cases of dilatation seems to be a loss of tone and a failure of contractility, arising either by the direct action of poisons or from exhaustion in consequence of

the excess of work being too great for the available quantity of muscle. Of cardiac tone we know practically nothing beyond what is suggested by the phenomena under discussion, which appear to be most readily explicable on some such hypothesis. This atonic dilatation may under suitable circumstances be accentuated by forcible distension, as already mentioned, in either ventricles or auricles. Though its existence is perhaps best shown by a consideration of the facts relative to ventricular dilatation, it occurs to a more marked degree and more commonly in the auricles.

When any cavity of the heart is enlarged, the muscle forming its wall is placed at a considerable mechanical disadvantage. An increase in diameter which may appear comparatively trivial means a considerable increase in contents, and the work which has to be done by the muscle at the beginning of its contraction, if the normal intracardiac pressure is to be maintained, is in the same way increased approximately with the cube of the diameter. Thus, to take an extreme case, if the auricle is dilated to twice its normal diameter, the muscle must be exerted eight times as much as before to produce the same pressure. It follows that any increase in capacity is potentially a powerful stimulus of hypertrophy. This actually occurs when the enlargement is compensatory to a demand for an increased output, and in such cases increase of capacity and muscular hypertrophy go hand in hand. But with forcible distension or atonic dilatation the hypertrophy often fails. With forcible distension, this is due to the fact that the increase of work put before the muscle is much beyond its utmost power; it has already been pointed out that hypertrophy does not follow such overwhelming stimuli, and the distension may be so great that the muscle is unable to contract at all. In atonic dilatation we have in addition the diseased or exhausted state of the muscle which has allowed the dilatation to arise, and which will certainly be a hindrance to hypertrophy. The result is that forcible distension or atonic dilatation generally means a serious degree of heart failure. In the case of the ventricles the condition is hardly compatible with prolonged life. The auricles, on the other hand, may for a long time be blown out to such a degree that they cannot contract at all to any propulsive purpose.

**The Valvular Mechanism.**—One of the common causes of increase of work in the heart is defect of the valvular mechanism. This may arise without any disease of the valves themselves. The proper working of the auriculo-ventricular valves depends not only on the integrity of the valve flaps, but also on the due support afforded by the cardiac muscle. Flabbiness and loss of tone of the muscle may therefore lead to incompetence of the mitral or tricuspid valves. It is doubtful whether the aortic and pulmonary valves are rendered incompetent by simple stretching of the fibrous rings on which they are hung; at any rate, the muscle is not concerned.

The great majority of cases of actual valvular disease fall into two groups, both inflammatory in nature. In the first place, acute inflammations, generally of the mitral, but commonly enough of the aortic valve, may be caused by many pathogenic bacteria. The coccus which is etiologically connected with acute rheumatism is the most important, both on account of its frequency and because the pericardium and myocardium are often severely affected as well as the endocardium, and hence difficulties are put in the way of compensation of the effects of valvular defects. Attacks of acute valvular endocarditis due to this cause are, moreover, liable to recur several times in the same person at intervals of months or years. Whatever the immediate cause, the valvulitis is commonly part of a general systemic infection. The organisms gain entrance from the capillaries in the heart wall at the root of the valve, through which they spread until they reach the free end. Once the endothelium is affected by the infection, mechanical considerations may come into play in determining the precise area in which the endothelium will be so far destroyed as to cause the separation of fibrin from the circulating blood on to the injured patch. For this reason the change is often concentrated a little short of the free edge of the valve—at the place, that is, where contact with the other segments on closure is liable to rub away endothelium of depressed vitality. Though the patient may at this stage be profoundly ill either in a general way from the existing septicæmia, or from the local affection of the cardiac muscle where such occurs, there is not necessarily anything very much wrong with the working of the valves themselves, unless the inflammation is so violent that extensive necrosis and perforation or rupture of a segment occurs. It is the reparative growth of fibrous tissue which takes place during the healing of the acute inflammation which produces the more serious results. This scarring may be localized to part of one segment, but in severe cases of rheumatic valvulitis the whole of both segments—speaking of the mitral valve—may be involved, together with the subendocardial connective tissue at their base. The slow contraction of this irregularly-shaped mass of fibrous tissue may produce the most varied results. Generally speaking, however, they are of two kinds: those in which the valves are shrivelled and more or less completely destroyed, and those where the contraction has also extensively invaded the tissues at their roots. In general correspondence, the functional effect may be either that the valve is incompetent during systole of the left ventricle, or it may be incompetent and at the same time the whole orifice be smaller than usual, so that there is an obstruction to the blood-flow from the left auricle. When there is definite narrowing of the auriculo-ventricular passage, the valve is probably always incompetent during ventricular systole. It is, however, customary to recognize as examples of mitral stenosis those cases where the

main difficulty with which the heart has to contend is a narrowing of the orifice rather than the regurgitation.

In the second place, the inflammatory change may be chronic from the outset. This is especially seen in the aortic valves, where it is generally syphilitic in origin. In the mitral valve some slight degree of thickening with fibrosis is common enough in those past middle life; its origin is obscure, and the effects on the working of the valve seem negligible. As far as the valves are concerned, the ultimate result is much the same with a chronic as with an acute inflammation. The changes produced by the latter are perhaps more definitely limited by the amount of damage done during the acute stage. The chronic changes tend to progress indefinitely, though, on the other hand, they probably proceed on the whole more slowly, and thus give a better opportunity for compensation.

The valvular defects so produced—and other causes beyond congenital malformations are so infrequent as not to require mention—may involve any valve. They are, however, much more common in the left heart than in the right, except in intra-uterine life, when valvular endocarditis seems to be equally common on both sides. The obvious suggestion which arises out of this is that the difference in the work to be done and in the intracardiac pressures in the right and left sides, which is established at birth, is the explanation of the alteration in the distribution of the lesions. If this be correct, it follows that we should consider mechanical strain as an important accessory factor in the causation of serious valvular defects in post-natal life. This is confirmed by our knowledge of the influence of hard work and a high blood-pressure in promoting syphilitic disease of the aortic valves, and of the prophylactic effect of complete bodily rest in minimizing the valvular distortion after an attack of acute rheumatic endocarditis.

The precise effect of the lesions varies with a number of conditions: the valve affected, the amount of injury, the time relations of the progress of the distortion and, most important of all, the capacity of the heart muscle to accommodate itself to the altered conditions by due hypertrophy. For this reason any valvular lesion is likely to be less serious in its immediate effects if the myocardium is young and healthy than if it is old and diseased. It would be an endless tale to discuss all the permutations and combinations of the effects of valvular mischief, and the principles which govern the behaviour of the heart under such adverse circumstances have been already considered. We may, however, take one example, and summarily trace the progress of functional incapacity in a heart in which there is a moderate degree of incompetence of the aortic valve. The left ventricle enlarges its cavity to increase its output, and increases its muscle because it has more work to do. These changes are fully compensatory,

and carry on the circulation in a normal manner—at any rate, so long as no undue call is made for extra work by muscular exertion, etc. The degree of incompetence, however, progressively increases, or other difficulties arise, such as disease of the coronary arteries, and hence interference with the nutrition of the hypertrophied muscle. The left ventricle then ceases to be able to pump quite adequately, and at this stage is liable to dilate to such a degree that it cannot contract at all, and thus life is suddenly brought to an end. If this does not happen—and with healthy muscle and normal arteries it is exceptional—the mitral valve loses support when the tone of the left ventricle fails, and becomes incompetent. It is probably at this stage that the circulation begins to definitely fail, since the ventricle cannot be large enough and have muscle enough to cope with both aortic and mitral incompetence, especially when the latter has arisen through muscular failure. The left auricle is then exposed to an increased pressure, which may arise comparatively suddenly, and reaches a degree beyond anything which auricular muscle has been accustomed to deal with. The auricle is distended, it may be, to such a degree that it contracts very imperfectly. This may not be very important as regards the filling of the ventricle, but at the same time the pulmonary pressure rises and the right ventricle has more work to do. It therefore hypertrophies, but the failure of this hypertrophy is not so long delayed as in the case of the left ventricle, because in the case we are considering the circulation is already not all that it should be, and hence the supply of food is unsuitable. When the right ventricle becomes exhausted and dilates, the tricuspid valve becomes incompetent, and the right auricle receives the right intraventricular pressure. Under these circumstances it is soon blown out, and brought to a standstill or a condition of ineffective twitching. The heart is now an altogether ineffective pump, and the muscle is liable to all sorts of irregularities of initiation, conduction, contraction and tone. By how much the circulation is slower than normal is quite unknown, but the general deficiency of oxygen-supply to the body at large is shown by the disordered working of the nervous system, stomach, liver, kidneys and other organs.

**The Pericardium.**—The parietal pericardium performs the same function as the outer cover of a bicycle tyre. Normally it is an unyielding fabric which prevents undue distension of the heart, especially in diastole. Changes of intrapericardial tension have an immense effect on the working of the heart. In animal experiments it is found that an increase of pressure by as little as one or two millimetres of mercury produces a considerable fall in arterial pressure by impeding the filling, and therefore the output, of the heart. A small fall in intrapericardial pressure has an equal effect in raising arterial pressure.* A pressure of 20 or 30 millimetres

* Lewis, *Journ of. Phys.*, 1908, vol. xxxvii., p. 213.

brings arterial pressure to zero. In human experience, a comparatively small hæmorrhage into the pericardial sac brings the heart to a standstill by hindering full diastole and by pressing on the coronary veins.

The only common and important disease to which the pericardium is liable is inflammation which follows the ordinary course of the process in serous sacs. At first the pericardium contains excess of fluid, some or most of which may soon become more solid by coagulation. The bulk of this may be considerable, very much more, for example, than is required, in the form of freshly effused blood, to stop the heart with a normal pericardium. The sac, in fact, becomes softened by the inflammation and more distensible. At this stage the heart is probably directly affected by the increase of pressure, and shows some signs of failure to fill properly. But it is hardly ever possible to disentangle the effects of the pericardial effusion from those of the myocardial, and perhaps also endocardial, affection which is present. The common causes of acute pericarditis are the pneumococcus and the rheumococcus. Both are pre-eminently organisms which in one way or another have an intense and specific poisonous action on heart muscle. Not only, therefore, is it difficult to distinguish that part of the muscular failure which is primarily pericardial from that which is primarily myocardial in origin, but the heart is itself commonly at a disadvantage in resisting the pericardial condition. The softening of the pericardium also allows the heart to dilate if the fluid is partly or wholly absorbed. Passive non-inflammatory effusions into the pericardium occur as part of the general dropsy of renal or cardiac disease. They appear to cause some, but not extreme, cardiac difficulty, but the conditions under which they occur are too complicated to throw any clear light on the effects of a chronic increase of pericardial fluid.

If the inflammatory process proceeds to a natural cure, organization of the effusion is effected by growth of the subpericardial connective tissue and vessels. The visceral and parietal layers are thus bound together. To some extent the heart by its constant motion may prevent the adhesion becoming extensive, but commonly enough the muscle becomes joined to the parietal pericardium by firm fibrous tissue over a considerable proportion, sometimes the whole, of its surface. The pericardium is fixed pretty firmly in the chest, above to the deep cervical fascia, below to the central tendon of the diaphragm. If the rest of the pericardium is cemented on to the heart, it can be seen how its natural movements are likely to be hindered. This will be more marked if, as often happens, the original inflammation has extended outside the pericardium in the connective tissue of the mediastinum (indurative mediastino-pericarditis). By this means the heart is tied to the sternum and lungs. It is not uncommon to find that

some of the larger masses of clot in the pericardium have escaped organization, and have been converted into hard calcified plates. In some instances the heart is surrounded by a series of such plates, which form a stiff box, to the interior of which it is firmly fixed. The precise motions which the heart, as a whole, undergoes during contraction are not fully determined; but, whatever they may be, it is clear that they cannot be properly carried out under circumstances such as these. The filling difficulty caused by the effusion is replaced by an emptying difficulty. Some degree of simple adhesion between the parietal and visceral layers may cause no obvious changes in the heart, but the more exaggerated conditions mentioned increase the work of the heart so much that, arising as they often do in young persons, they bring about some of the most extreme degrees of hypertrophy of the whole heart.

**Cardiac Reflexes and Sensations.**—The nervous connection between heart and respiration is shown by a variety of phenomena. The whole of the respiratory apparatus constitutes a field, stimulation of which may give rise to alterations in cardiac action of a more special kind than those observed in response to the stimulation of afferent nerves in general. The receptive sensibility varies in different parts, but stimulation anywhere from nose to pleura may cause complete reflex cardiac inhibition. In this way sudden death may follow the inhalation of irritating vapours or the introduction of a trochar into the pleural cavity to remove an accumulation of fluid. Conversely it has been shown that respiration may be inhibited by stimulation of the endocardium, and it is possible that some of the abnormal respiration of cardiac disease is due to this association. Slight irregularities of heart-beat may give rise to sensations which are, as far as can be judged, purely respiratory. It is impossible to exclude altogether the effect of the alteration in the aeration of the blood on the respiratory centre, but it seems more likely that the "gaspy feeling" which may occur with a single dropped ventricular beat is due to the close nervous association of the cardiac and respiratory apparatus. The alterations of pulse-rate with varying phases of respiration may fall under the same head. We have here, however, to consider the possible effect of changes in arterial pressure.

A rise of arterial pressure causes a slowing in the rate of beat; an increase of intracranial tension causes both a rise of pressure and a slower beat. The heart is sensitive enough to changes of intracardiac pressure. A rise of pressure acting on isolated cardiac muscle seems, however, to stimulate it to greater activity, and the protective slowing is no doubt a reflex effect through the vagus centre. Though little is known about it in man, we have in animals a very powerful mechanism for reducing arterial pressure, the afferent path of which starts in the heart and runs in the depressor nerve.

Sensory impulses of all kinds, whether represented in consciousness or not, are liable to produce effects on the heart-beat. The common result of sudden emotion is a short slowing, perhaps amounting to a standstill, followed by a more prolonged accleration. Very painful sensory stimuli may stop the heart for good. Under such circumstances the heart may be reached through the nervous system, or through the circulation (arterial pressure, coronary circulation or quality of blood), and it is not possible to say in all cases what the communication is.

The vagus centre may be directly stimulated, as by chloroform, or reflexly, as by pleural stimulation or a high arterial pressure; but the heart seldom suffers from disease which primarily affects either the medulla or the vagus. When one vagus is divided or ligatured in the neck, there is generally manifest disturbance in the shape of slowing and irregularity of heart-beat; it is, however, transitory. Degeneration of the inhibitory, trophic and tonic fibres of the vagus has been suggested as a cause of the irregular rate and liability to dilatation seen in diphtheria and some other infections which bring about neuritis.

The real basis of *palpitations* is obscure. Some persons often, and most people sometimes, become aware of the fact that their heart is thumping on their chest wall. This is more marked if the heart is hypertrophied, and in any case the action seems to be unnaturally forcible, and is sometimes irregular. The violent and rapid contractions produced by muscular work are usually fairly obvious, and overaction of the heart may be the chief cause of palpitations rather than increased sensibility.

A slight degree of *pain*, referred to the præcordium, is not infrequent with diseased hearts, especially in mitral stenosis and aortic regurgitation. By gradations which appear to show no clear line of demarcation, these cases pass on to examples of the classical *angina pectoris*. Here we have attacks of the most extreme anguish, sudden in onset, often recurrent, referred to the axilla and inner side of the left arm as well as to the chest. The cardinal points which require explanation seem to be the pain, the fact that the patient generally dies in an attack sooner or later, and the observation that relief may often be obtained by amyl nitrite. It is also probably a significant point that severe attacks usually occur in persons whose hearts are not obviously and grossly diseased, and are working so reasonably well that they satisfy the requirements of an ordinary active life. Attacks cease if chronic heart failure arises. During an attack the pulse may be slower, faster or perhaps irregular; but on the whole there is very little alteration. Post-mortem results show no uniform or specific change. The heart may appear quite normal, with or without syphilitic disease of the root of the aorta and the valves. Most commonly there is some obstruction of the coronary arteries, narrowing of the orifices

by aortitis or arterio-sclerosis, and perhaps calcification, which may be generalized or quite local; angina may also be caused acutely by embolism of a small branch. Some change in the heart muscle in the way of fibrosis is thus to be expected in many cases, and generalized arterio-sclerosis with abnormally high arterial pressure is usually present. These changes are much more often seen in persons who have not shown angina during life. They are, however, notorious causes of sudden death, and no doubt many persons can give no history of severe cardiac pain because they die in the first attack. Taking all these points into consideration, it is reasonable to conclude that angina is due to a violent stretching of the cardiac muscle. Considerable distension of any muscular viscus is liable to be extraordinarily painful, and it is known that the same is true of the vascular system as far as the arteries are concerned. It may well be that the stretching of the heart wall is not uniform. Local changes are associated with the disease, and the fact that the heart must be, on the whole, in good general condition suggests that the healthy muscle of the left ventricle raises the pressure beyond the point that a diseased, fibrotic area can stand without being forcibly stretched. Otherwise it is not altogether easy to see where the distending force comes from in the absence of valvular disease, though the efficacy of vaso-dilation in relieving the spasm suggests that the heart is failing to empty itself against a high aortic pressure. There are many objections to this view, and it does not necessarily follow that amyl nitrite gives relief because it lowers arterial pressure. The heart may stop owing to the distension, or it may be that it is reflexly inhibited by the very severe pain. The actual cause of death may be cessation of respiration, which is no doubt caused reflexly.

**Respiration and the Circulation.**—The negative intrathoracic pressure is of great importance in helping to fill the heart in diastole, though the circulation still proceeds when it is abolished. Its influence is naturally greater on the thin-walled auricles than on the ventricles. It is more marked when the respiratory movements are exaggerated, as in hyperpnœa and dyspnœa, though it does not appear that the negativity of pressure is ever great enough to seriously impede the contraction of the ventricles and the emptying of the heart. On the other hand, the sucking action of the lungs on the heart is reduced when the respiratory movements are diminished, when the elasticity of the lungs is, as in emphysema, impaired or destroyed, and when the pleura is filled with air (pneumothorax) or liquid (pleural effusion). If respiration stops, as in the apnœic periods of Cheyne-Stokes breathing, there is a notable fall of arterial pressure. If the intrathoracic pressure becomes actually positive, the diastolic filling may be very much obstructed. The blood cannot get into the heart from the veins, and the ventricles may have nothing to pump. Such an increase

of pressure occurs when forcible expiration is made with a closed glottis or with obstructed expiration due to changes in the air-passages, and when the whole thorax is compressed by external violence. The influence of changes of pressure caused locally in the pericardium has already been mentioned.

It is not clear that the physical effects of the heart-beat on pulmonary ventilation are of any importance. A hypertrophied heart takes up an abnormal amount of room in the chest, and causes more ample cardiopneumatic movements. It is possible that the sudden movements so produced are of some moment in helping the passage of air along the smaller tubes.

Respiration affects the circulation not only by its influence on the filling of the heart, but by the aid which it gives to the passage of blood from the right to the left heart by the alternate expansion and compression of the pulmonary capillaries. With a fall of intra-thoracic pressure, the capillaries are expanded, while a rise of intra-pulmonary pressure, as in coughing, compresses them. In man an intercostal inspiration gives a fall of blood-pressure; diaphragmatic inspiration, owing to the increase of intra-abdominal tension, causes a rise.* By a reflex mechanism, the heart beats more slowly and more amply during the latter part of expiration and at the beginning of inspiration. The total effect of these various factors is very complex under different circumstances, but there is no doubt that active respiratory movements are of distinct advantage in getting a large volume of blood through the heart, and not allowing the blood to gravitate to the most dependent parts, while an unduly quiet respiration allows the pulmonary circulation to become more or less stagnant. The ill effects of stopping in bed are liable in this way to fall on the lungs.

**Diseases of Arteries.**—Our knowledge of arterial disease is not a little confused, especially as regards the relationship of the different changes to one another. Before discussing, therefore, the effects of morbid conditions on the circulation, it will be well to briefly summarize some of the commoner and more definitive alterations in structure.

1. *Senile Degeneration.*—In old age it not infrequently happens that the middle coat, and to a less extent the deeper layers of the intima, are the seat of extensive calcareous deposit. The change involves especially middle-sized vessels—*e.g.*, the radial artery or the circle of Willis—and appears to begin in a degeneration of the muscular fibres. The early stages of this change in the media are common enough, and are from the first associated with some degree of calcification. In more advanced cases most of the wall may become involved, and the artery be converted into a rigid tube.

* Lewis, *Journ. of Phys.*, 1908, vol. xxxvii., p. 233.

2. *Endarteritis* is a condition involving quite small vessels. There is an overgrowth of the subendothelial connective tissue of the intima, which may almost occlude the lumen. It occurs in cases of disuse atrophy of arteries—*e.g.*, in the uterine arteries after childbirth—and in association with many infections—*e.g.*, glanders, typhoid. Pre-eminent among the latter is syphilis. Endarteritis is a highly characteristic part of the tissue reaction to the *Spirochæta pallida* in all stages of the disease, from the primary chancre to the late gumma.

3. The aorta and other large arteries are subject to another important syphilitic affection—*syphilitic arteritis*. This condition is essentially a gummatous arteritis. The whole thickness of the vessel wall is involved. There are grounds for thinking that the adventitia is first attacked. However that may be, in its active stage we find more or less extensive destruction of the proper tissue elements (muscle and elastic fibres), with overgrowth of white fibrous tissue, vascularization and focal accumulation of lymphocytes and plasma cells. The intima is least altered, and the endothelium remains intact. As the inflammatory process progresses, the new-formed connective tissue contracts and forms a fibrous scar in the wall of the vessel. Such a scar is stiff, and lacks the elasticity which the normal vessel wall possesses in virtue of its muscle and elastic fibres. It is this rigidity which renders the condition of great practical importance, since the scar is liable to stretch and give way, and hence allow the formation of an *aneurism*. There is little doubt that the most frequent cause of the ordinary aneurism of the aorta is syphilitic aortitis.

4. *Atheroma*.—By atheroma we understand a very common disease of the aorta and larger arteries characterized by the occurrence in more or less localized patches of (1) overgrowth of the intima: the projecting mass formed in this way is often degenerated in the centre, *i.e.*, in the part most remote from its blood-supply; (2) degeneration of the underlying media, with destruction of muscle fibres and calcareous deposit; (3) in advanced examples the greater part of the proliferated intima degenerates, the endothelium is destroyed, and the inner surface of the vessel is, at that particular point, formed by the calcified débris of the deeper parts of the intima or more superficial layers of the media. The natural history of the disease, and especially the relation of the intimal to the medial change, are obscure. The views which have been advanced fall into two main groups. According to one, the intimal change is primary. There is localized overgrowth of the subendothelial tissues similar to the more widely spread proliferation in the endarteritis of smaller vessels. At the same time degenerative processes begin, and subsequently involve the whole of the intima and spread more or less deeply into the middle coat. The other view is that the essential change is a destruction of patches

of muscle in the media. The loss of substance thus produced is made good by the growth of the intima, which subsequently degenerates owing to its bad blood-supply. The area of necrotic, fatty and calcareous tissue which arises in this way may become confluent with that produced by the extension of the original mischief in the media. According to this interpretation, the nodules of overgrown intima which are found post mortem projecting into the lumen of the aorta are during life not raised above the surface, but fill up the deficiencies of substance in the arterial wall caused by destruction of media. Such a view brings the overgrowth of the subendothelial connective tissue into line with our general conceptions of the reparative, compensatory proliferation of white fibrous tissue by which any odd holes in the body are apt to be filled in. It is also in accordance with experimental evidence. In some instances, at any rate, the nodules of early atheroma, which are seen as elevations on the wall of the aorta after death, no longer project into the lumen when the vessel is distended with an internal pressure equal to that which obtains during life. The notion that the primary change is in the middle coat is also supported by the fact that slight degrees of degeneration and calcification of the muscle fibres are extremely frequent in middle-aged and elderly persons whose aortas show no signs of disease of the intima. It is equally true that patches and lines of purely intimal degeneration, characterized especially by the accumulation of fat, are common enough. These are, however, found mostly in young persons, and it is clear that definite atheroma is, with rare exceptions, a disease of adults.

A condition which is probably identical with human atheroma may be easily produced experimentally in herbivorous animals. Repeated doses of substances which cause a marked rise of blood-pressure, such as adrenalin, nicotine, or barium salts,* bring about a patchy degeneration of the media with fatty and calcareous change in the muscle and elastic fibres.† The substances mentioned are highly toxic, and it might be that the changes produced are not entirely due to their pressor action. It has, however, been shown that the same changes may be brought about by compressing the abdominal aorta in rabbits for a few minutes every day for some weeks. Direct experimental evidence is thus afforded that the medial changes may be caused by heightened blood-pressure. It is reasonable to think that the muscle and elastic fibres are directly ruptured by the increase of pressure. It is a general opinion, which may or may not turn out to be true on more accurate inquiry, that atheroma in man is associated with modes of life

* Rickett, *Journ. of Path.*, 1908, vol. xii., p. 15.

† Aneurismal dilatations are often produced in animals, whereas they are infrequent in human atheroma—a difference probably due to the rate of production.

which entail frequent and considerable elevations of blood-pressure —lives, that is, in which severe muscular efforts are frequently made. Note also that the vitality and elasticity of the aorta progressively diminish with advancing years, so that the fibres break more easily under strain.

It seems, therefore, probable that atheroma of the aorta is essentially a disease of the middle coat caused by the stress of an excessive blood-pressure. But it is hardly likely that the tale is really as simple as this. Atheroma shows a curious distribution among individuals. Every disease has its individual variations, and the resistance of the muscle fibres doubtless varies in different persons ; but the fact that atheroma may be produced experimentally by the repeated injection of bacillary toxins suggests that similar circumstances may play a not inconsiderable rôle in man. Apart from a general tonic effect on the muscle, infections may determine the incidence of atheroma through an endarteritis, generally syphilitic, of the vasa vasorum.

Atheroma is not restricted to the aorta. Similar changes, as a rule of a less pronounced degree, are also seen in other large arteries, such as the carotid and femoral. The tendency is, however, for these to be more intimal overgrowth and less medial degeneration and calcification than in the aorta. In still smaller vessels we may find intimal overgrowth by itself. Whether this latter be atheroma, and, if not, where we are to draw the line of demarcation for that disease, is very uncertain. It is, however, known that conditions which in animals produce medial degeneration in the aorta may in the carotids cause only an overgrowth of intima. It has been suggested that this difference is due to the greater abundance of muscle in the carotid wall and to the smaller lumen. The wall can therefore withstand a greater stress without actual rupture, and the general increase of lumen which a rise of blood-pressure tends to cause is compensated by an overgrowth of the subendothelial tissue.

5. *Arterio-sclerosis.*—The changes which occur in the smaller vessels in apparent causal relation to high blood-pressure bring us to the consideration of arterio-sclerosis. The term is vague, and is used in many different senses, partly anatomical, partly clinical. It is perhaps best to look upon it as signifying a condition in which the arteries feel thick and stiff, with special reference to their apparent texture during life. After death the lumen of arterio-sclerotic vessels is abnormally small, but it is doubtful whether this condition obtains during life. It is certainly associated with high blood-pressure. The underlying anatomical change is various. In the first place, the vessel may be harder to feel without any very definite anatomical change. The stiffness of an artery—that is, its resistance to alterations in calibre—varies a great deal in apparently similar arteries from different individuals, and in the

same artery according to the state of tone of the muscle fibres. On the whole, though with marked individual exceptions, the arteries become stiffer as the individual grows older. The condition of tone also varies in different people and at different times, chiefly in response to the stimulation afforded by an increase in blood-pressure. In the second place, we may find in such hard arteries definite structural changes. These consist in the main of an increase in the middle coat, involving muscle and elastic tissue ; the muscle fibres may be to some extent degenerate and calcareous, or show hyaline change, and in some instances there is intimal overgrowth as well as an increase in the fibrous tissue of the outer coat. It is probable that the increase in the intima, and such retrogressive change as is found in the media, should be regarded as indications of an accompanying atheroma. Arterio-sclerosis, like atheroma, is without much doubt the direct result of an increase in blood-pressure. The two conditions, however, do not necessarily occur together in the same individual, and there are grounds for thinking that the increase of pressure which tends to produce arterio-sclerosis is persistent, while that which ends in atheroma is intermittent. The overgrowth of muscle seems to have a different origin. The increase of mean blood-pressure which comes on in many individuals as they approach middle life, and slowly progresses to reach, in the least favoured, nearly twice the normal level, stimulates the arteries to contract, and ultimately leads to a very definite overgrowth of muscle (*arterial hypermyotrophy*), without which the vessels would be passively distended. That the response to an increase of blood-pressure is hypertrophic in small arteries and destructive in large vessels may depend on the size and relative bulk of muscle and elastic tissue in the two cases. It seems, however, more likely that the causative factor is, as already indicated, not quite the same.

Briefly, then, arterio-sclerosis includes increase of rigidity (due to age), increase of muscle (due to high blood-pressure), and degenerative changes in media with overgrowth of intima (which is atheroma). The co-existence of these changes in varying proportions leads to anatomical results which are not a little complicated, so that some have concluded that the whole should be grouped together with aortic atheroma as a single disease (atherosclerosis).

**Occlusion of Arteries.**—Apart from the deliberate interference of the surgeon or the experimentalist, arteries are commonly obstructed from within, though pressure from outside, as by tumours, may sometimes produce the same result. The walls of the vessel may simply come together and obliterate the lumen of small arteries. This is well seen in the case of vessels which have been developed or have become much enlarged in order to bring blood to an area of long-continued active inflammation. When

repair has been effected, the abundant blood-supply is no longer needed, and, doubtless by the action of the vasomotor apparatus, the useless vessels cease to be patent. Vasomotor spasm may also close vessels functionally though not structurally (p. 314). Active overgrowth of the vessel wall itself often leads to almost complete obliteration—*e.g.*, syphilitic endarteritis—but not so frequently to total closure, unless clotting of the blood inside is superadded. Clotting of blood (*thrombosis*) may of itself block an artery, or the vessel may be obstructed by the transport of plugs of various kinds from other parts of the vascular system to a place where they stick either at the bifurcation of a vessel or by reason of a diminution in calibre (*embolism*). Thrombosis is dealt with elsewhere (p. 38). We may here, however, note that the whole or part of a clot may be detached and plug another vessel—*i.e.*, a *thrombus* may form an *embolus*—and that the partial blockage produced by an embolus may be made complete by superadded thrombosis.

*Emboli* may consist of any solid mass, and some fluid substances, which gain entrance to the vascular system. They may originally arise (1) within the vessels, as in the very common cases of the detachment of parts of thrombi which have formed on the cardiac valves or in the uterine or femoral veins; (2) within the body, but outside the vessels, as in the case of bits of malignant growths which have invaded veins, and liver cells or fat after injuries to the liver and bones respectively; or (3) outside the body altogether, as in the case of air entering through wounds of the great veins near the chest. Emboli arising in the portal system commonly lodge in the liver; pulmonary embolism is due to bodies taking origin in the systemic veins, while emboli in the systemic arteries generally come from the heart itself. This, however, appears to be only true because the commonest embolus which causes obvious effects—and of any other emboli hardly anything is known—is a piece of clot formed in the left heart in the course of a valvular endocarditis (p. 291). This must necessarily be distributed to the systemic arteries. There is no doubt that the passage of small emboli from the veins through the lungs is of not infrequent occurrence. Small emboli consisting of liver cells, cells of malignant growths which can be identified with certainty and air undoubtedly get from the veins to the systemic arteries with a frequency which cannot be explained by the occurrence of patent foramina ovalia.

It is convenient to look upon arteries as existing for the purpose of bringing blood to the tissues. As far as the tissues are concerned, the great majority of emboli produce no drastic effect. The anastomoses between arteries are so abundant that hardly any part of the body is dependent on a single channel of supply. In consequence, almost any moderate-sized artery in the body may be tied, or otherwise closed, with impunity. The anastomotic channels immediately dilate up and bring an adequate amount of blood to

the tissues which naturally receive their chief supply through the occluded vessel. Under certain circumstances, however, death of larger or smaller pieces of the body follows. The mass of dead tissue so produced is commonly called an "*infarct*" when it is produced by an embolus; to the same condition in the central nervous system the term "softening" is usually applied; while if a considerable piece of the external parts of the body is similarly affected we say there is "gangrene" of, *e.g.*, the foot. It is important to be clear on the one hand that these terms all denote conditions which are essentially the same, and on the other that infarction, softening and gangrene are not always and exclusively produced by arterial obstruction.

The conditions which determine the survival of tissues so deprived of their normal blood-supply must next be considered. *A.* (1) The presence of anastomotic channels is essential. In most parts of the body these are abundantly present, in others they are imperfectly developed (parts of the central nervous system, kidney, myocardium), while in the case of the pulmonary artery they seem to be absent. The possible paths by which blood might get to any tissue may also have been reduced by disease before the main supply is blocked by an embolus or otherwise. (2) It is also necessary that these anastomotic channels should be of sufficient calibre to carry the necessary amount of blood. In the kidney, for example, obstruction of a branch of the renal artery is followed by death of the tissues supplied, the anastomoses with the lumbar arteries in the capsule being altogether inadequate to bring enough blood to the cells. (3) The effects also vary with the condition of the arteries. Old sclerotic vessels have little capacity for vasomotor adjustment and dilatation, and, in cases where the vessels are diseased, ligation of, *e.g.*, the femoral artery may be followed by death of the limb, though the anastomotic channels here are normally of macroscopic dimensions. *B.* Besides these factors concerning the blood-supply, we have also to consider the susceptibility of the tissues to deprivation of blood, regarded on the one hand as a matter of degree, and on the other hand as a matter of time. The nerve cells of the central nervous system are extremely sensitive to lack of blood. A short stoppage of the blood-stream may produce not only a temporary cessation of activity, but also irreparable damage and death. Sudden occlusion of one common carotid in man is sometimes followed by death from cerebral anæmia, and usually produces quite definite cerebral symptoms, although the collateral supply is very large. The secreting cells of the kidney have a sensibility of the same order. If the renal artery be compressed for a short time, the kidney will not secrete any urine; on the restoration of the supply the cells of the convoluted tubules will be damaged beyond recovery. Under the same circumstances the connective tissue and glomerular cells

may survive, showing clearly the difference in susceptibility of the various tissues. On the other hand, some tissues, such as periosteum, are able to survive an anæmia lasting many hours. Except in the case of air embolism, the stoppages of arteries which occur in the natural course of disease tend to become worse rather than better—at any rate, for the first few days. The time factor therefore is important, not because there is much chance of the block becoming undone, but in relation to the dilatation of the anastomotic channels. The flexibility of the vasomotor apparatus is an important factor, and there are reasons for supposing that this is unequally developed in different parts of the body. *C.* We have finally to consider the influence of the events which may occur in sequence to the cessation or partial cessation of the obstruction, whether this be an actual removal of the block or, which amounts to the same thing, a functional removal brought about by the opening up of the anastomotic supply. The temporary anæmia is succeeded by marked hyperæmia. As a result of the starvation of the tissues and the capillary walls, an outpouring of lymph and blood takes place, and a condition of complete and relatively permanent anæmia may be again produced by the pressure of the extravasated fluids. The degree to which this extravasation takes place varies in different parts, being most marked in loose tissues, such as the intestinal mucosa and submucosa. Another phenomenon of a similarly indirect kind appears to come into play in the production of local death of the intestine after occlusion of the mesenteric arteries, in spite of the free anastomotic supply. The initial anæmia produces a spasm of the muscular coats, which compress the smaller vessels. Necrosis is then accelerated by the proximity of the mass of bacteria in the bowel.

The point of practical importance is whether the tissues normally supplied, wholly or in part, by the obstructed vessel are killed or not. From the above considerations it will be apparent that it is not necessary to discuss at length which arteries in the body are truly "end-arteries" in the sense that they have no anastomoses. These anatomical matters are to some extent unsettled, and doubtless there is a good deal of individual variation. But we may note here the vessels which have been found by experience to be functional end-arteries. These are as follows: the basal arteries of the brain, the arteries of the central nervous system after they have penetrated the substance of the brain or spinal cord, the central artery of the retina, the renal and splenic arteries, the intramuscular branches of the coronary arteries, the mesenteric arteries, the portal vein and pulmonary artery. In these instances infarcts may be produced, but in none of them can we positively affirm that blocking is invariably followed by death of the tissue supplied, since it is almost always the occurrence of necrosis that directs our attention to the question of the patency of the vessel. When, however, we

find infarcts in the kidney and spleen, and in no other organ, due to pieces of clot which have been detached from an inflamed cardiac valve, we are justified in assuming that the emboli must have been distributed pretty uniformly all over the body, and in concluding that many arteries must have been blocked without giving rise to any massive destruction of tissue. Since in such cases most of the infarcts are in one or two organs (kidney, spleen), it seems probable that blocking of a number of the arteries named above must occur without causing such an amount of necrosis as attracts attention. In some instances general death follows embolism so soon that there is no time for the development of those post-mortem changes in the dead area of tissue which render it conspicuous. This is seen in embolism of the pulmonary artery in its larger divisions, and of the myocardium.

The effects of emboli vary with their nature and composition as well as with the site in which they lodge. Thus, a distinction must be made between sterile and infected emboli. A thrombus full of pyogenic organisms is particularly liable to give off emboli owing to its soft consistency, and in this way masses of organisms may be distributed about the body. At their points of lodgment—and note that the nature, situation and condition of the vessel is here largely immaterial—they may set up fresh foci of suppuration. This produces further thrombosis, from which a fresh lot of emboli may originate. The vessel wall may also be involved, being softened and perhaps dilated ("mycotic aneurism"). It is customary to restrict the term "infected emboli" to such as give rise to local changes in which the effects of bacterial activity overshadow those due to vascular obstruction. The common emboli of cardiac origin, for example, which usually contain bacteria in abundance, as a rule cause no obvious change beyond those due to arterial blocking. They are not classed as infected. In many bacterial infections small bacillary emboli doubtless often occur. Among protozoan parasites, obstruction of small intestinal vessels by the malaria organism may cause patches of necrosis, and a similar condition widespread in the brain may produce grave cerebral anæmia. Macroscopic animal parasites (*Trichina*, *Ankylostoma*) are also transported by the blood-stream, and ultimately stick in the muscles, lungs and other organs. Emboli consisting of fragments of solid malignant growths or of the semisolid sarcoma known as leukæmia differ materially from such bland emboli as drops of fat in the effects they produce, in that they are capable of setting up fresh centres of growth. In some tissues—*e.g.*, voluntary muscle—these malignant emboli are nearly always strangled and make no headway; in other places—*e.g.*, liver—they grow with greater facility. It would be out of place here to discuss the meaning of this curious distribution, which varies a good deal with the organ in which the original tumour arose. It will suffice to point out that it is quite

independent of any question whether the embolus sticks in an "end-artery" or in one freely provided with anastomotic channels. Thus active growth is very rare in the spleen, and, except with certain types of sarcoma, distinctly uncommon in the kidney.

*Air*, or, better, *gas*, *embolism* differs from other varieties in several details. Gas may be produced in the tissues and within the vessels both before and after death by the activity of *Bacillus aerogenes capsulatus* and allied organisms. It is, however, doubtful whether this ever obtains entrance to the circulation and causes emboli, since the areas in which it arises commonly have their vessels already isolated from the general circulation by inflammatory thrombosis. Atmospheric air may be sucked into the circulation through any hole communicating with those parts of the veins in which there is a negative pressure, most frequently in wounds of the great veins in the neck and axilla, and in operations about the pelvis. Air may also be forced into the pulmonary capillaries by an increase of intrapulmonary pressure, such as may occur in severe dyspnœa, especially if expiratory efforts are made with closed glottis. The most extreme degree of air embolism is found on rapid decompression after exposure to increased atmospheric pressure. While the body is in compressed air (diving, caisson work) the blood and tissues dissolve an excess quantity of air in proportion to the degree of pressure and the duration of exposure. If the return to normal atmospheric pressure is made too quickly, this extra gas is liable to be set free inside the vessels in the form of bubbles (composed chiefly of nitrogen) before it can escape by diffusion through the lungs, just as soda-water bubbles when the pressure is released. The symptoms of "caisson disease" are due to these bubbles. Death is usually produced by pulmonary embolism. It requires a relatively enormous pressure to drive a mixture of liquid and gas through a fine-bored tube, and the capillaries of the lungs are effectively stopped. A number of small bubbles, however, pass through into the systemic arteries, as is particularly well shown by experimental injection of air into veins. The emboli which in this way are distributed all over the body differ from those already considered in that they become smaller from the first, and many of them are redissolved in a comparatively short time. The result is that infarcts are not found in, *e.g.*, the spleen and kidneys, but are almost confined to the spinal cord, where the bubbles persist longer and the tissues are especially delicate. With solid emboli which persist, and, if anything, tend to increase in size from secondary thrombosis, the distribution of infarcts is quite different, the kidneys and spleen being affected far more frequently than the spinal cord. In connection with gas embolism, it is necessary to draw attention to the ease with which air may be drawn into the veins, and actually into the heart, during

the manipulations incident to a post-mortem examination. Much caution is necessary before concluding that a few bubbles found after death were in the circulation during life.

**Blood-Pressure and the Vasomotor Apparatus.**—The only methods available for the determination of the blood-pressure in the larger arteries in man are those in which a measured pressure is applied to a limb (usually the upper arm), so as to vary the lumen of the artery; the alterations in the peripheral circulation (the radial artery at the wrist) may then be observed. There is one point, at any rate, which may be accurately determined in this way—viz., the pressure necessary to obliterate the pulse beyond the point of compression. This figure must represent the maximum systolic blood-pressure within the vessel *plus* the resistance to deformation presented by the vessel wall. This latter counts for something, and for more when the pressure is high and the vessel wall contracted than with a low pressure and a lax artery;* but there seem no reasons for doubting that blood-pressure may be determined in man with substantial accuracy in this way. The normal pressure in the brachial artery of reasonably healthy young adults at rest is found to be somewhat more than 100 millimetres mercury. Any figure from about 95 to 120 millimetres can be regarded without undue suspicion. The variations associated with the common circumstances of life must, however, be carefully noted. The erect posture, bodily or mental activity, cold, for example, all tend to raise the pressure. Warmth and general lethargy have the reverse effect.

Blood-pressure is maintained at the required height on the one hand by the output of an adequate quantity of blood by the left ventricle, on the other by the due regulation of the outflow through the arterioles by the vasomotor apparatus. Within limits, irregularities in one of these factors may be compensated for by the appropriate variation of the other. Thus, some relaxation of the arterioles may not be followed by any considerable fall of blood-pressure, owing to an increase in the output of the heart. This is the condition found, for example, in active muscular work, where it is desirable that the blood should go round the body as quickly as may be, while it is at the same time necessary that its distribution should be pretty uniform. Again, the gravest mechanical defect in the heart—*e.g.*, mitral stenosis—is compatible with the maintenance of a normal blood-pressure. The diminished output is partly, perhaps, avoided by cardiac compensation, but it is for the most part corrected by peripheral vaso-constriction. The volume of fluid within the vessels has practically no influence on blood-pressure. Extensive hæmorrhage or the injection of large quantities of bland fluids into the circulation have, by their direct action, only momentary effects in lowering and raising pressure respectively, and in conditions of plethora (p. 22) we find that the

* Stevenson, *Journ. of Path.*, vol. xiv., p. 466.

volume of circulating blood may be three or four times the normal without any corresponding alteration in pressure.

In a general way, it is the business of the heart to see that the proper quantity of blood is circulated, and the business of the vasomotor apparatus to look after the blood-pressure and regulate the distribution of blood about the body. Their desiderata are to some extent incompatible. It is, for example, much easier for the circulation to proceed actively if the pressure is low. A high blood-pressure is, however, necessary in terrestrial animals to enable the vasomotor mechanism to direct the blood as required to different parts. We find in consequence that the heart actually has a relatively small share in pathological alterations in blood-pressure, compared to that taken by the vasomotor apparatus. No case is known where an abnormal increase of pressure is due to excessive cardiac action, and, though temporary cessation of the heart-beat leads, of course, to a definite fall of pressure, there is no association between low pressure and a cardiac action which is continuously imperfect or weak. In any case, attempts on the part of the heart to vary blood-pressure are as a rule easily frustrated by vasomotor action.

Inhibition of the tonic activity of the vaso-constrictor centre leads to a great fall of blood-pressure. This is commonly brought about in man by emotional causes, severe pain, and the like. The fall of pressure is such that the brain no longer receives an adequate supply of blood, and the person "faints." *Fainting* is sometimes caused by reflex cardiac inhibition. While in the erect posture the blood gravitates into the lower parts of the body, where the dilated arterioles readily admit it to the large veins; but as soon as the body lies horizontally the normal distribution of blood is resumed, the brain receives more blood, and consciousness is restored. There are many people with somewhat irresponsive vasomotor arrangements who feel faint and dizzy on rising suddenly from a recumbent to an erect position. The low blood-pressure, which does well enough when lying down, is not raised quickly enough to the level which is wanted when standing up, and there is in consequence a transitory cerebral anæmia. Similar phenomena occur when general vaso-dilation is brought about by amyl nitrite.

The state of *shock* is accompanied by a grave fall of blood-pressure, values as low as 30 to 40 millimetres Hg being observed. Shock is a condition in which all the functions of the body seem to be brought to a very low state of activity; respiration, the heart-beat, secretion of urine, etc., are all feeble, and may stop altogether. It generally follows considerable mechanical disturbance of the body, most often severe surgical operations. There is some uncertainty as to the exact mechanism whereby shock is produced, as there is also doubt as to whether the primary failure of function concerns the respiratory or the circulatory apparatus.

The exaggerated respiration caused by painful stimuli or by an anæsthetic tends to wash out too much carbon dioxide from the body, and so upsets the respiration.* Products of metabolism, of which carbon dioxide is not the least important, doubtless also have a direct influence on cardiac activity. Even if they do not, in a condition of feeble respiration or actual apnœa, the circulation loses the assistance of the respiratory pump. Be the share of respiratory failure in the causation of shock what it may, there is little doubt that the low blood-pressure is one of the most important, if not practically the sole, factor in the immediate causation of the symptoms. One may well imagine that a mass of painful impressions reaching consciousness from a mangled limb, or reaching a brain where recognition of consciousness is much distorted, qualitatively or quantitatively, by an anæsthetic during the operations of the surgeon, may give rise to a condition of fainting of a very exaggerated degree and a much prolonged duration. A fall of blood-pressure would hardly appear to be *per se* a sufficient explanation of the symptoms which seem to indicate a definite circulatory failure. This is produced by the action of the excessive fall of pressure on the heart, which loses thereby the stimuli of internal tension and pressure in front as well as an efficient coronary circulation. Experience has shown that direct stimulation of the cardiac muscle is of little use in the treatment of shock. The condition is not one of primary cardiac failure, and normal cardiac action may be restored by stimulating the vaso-constrictor apparatus by adrenalin and the like, and so raising the blood-pressure. The blood becomes diluted and increased in volume during shock.† It is distinct assistance in restoring blood-pressure if this compensatory adjustment is assisted by adding still more fluid by transfusion of blood or the infusion of salt solution. The injection of fluid into the vessels during shock raises blood-pressure. The absence of effect under normal conditions has been already noted.

With regard to persistent states of low blood-pressure, we have to note that, though some diminution may accompany many illnesses, one cannot definitely associate a state of "lowness" with a low blood-pressure. This curious condition goes rather with a variable, unstable pressure, and one which is easily influenced by comparatively trivial circumstances. The only pathological state in which a definitely low pressure is known to persist for months, or perhaps years, is destruction of the medulla of the suprarenal capsules (*Addison's disease*)—a circumstance which affords the only clear proof that adrenalin is constantly being produced in the body, and used to keep up blood-pressure. It is interesting to note that the arterial pressure in many cases of Addison's disease keeps somewhere about 70 millimetres Hg.

* Henderson, *Amer. Journ. of Physiol.*, vol. xxi., p. 126.

† Mummery and Symes, *Brit. Med. Journ.*, 1908, vol. ii., p. 786.

This seems to be quite enough to go on with quietly, and probably represents the mimimum necessary to maintain the capillary flow, the other 30 or 40 millimetres which a normal person has being for use in emergencies and to carry out the refinements of distribution. There is not necessarily a steady and progressive fall to the level found, for example, in shock, and there are no good grounds for thinking that death is directly due to the low pressure. Small quantities of adrenalin-producing tissue are scattered about the body in the carotid gland and elsewhere, but these chromaffine cells do not appear to play any part, by way of compensatory hypertrophy or otherwise, in the pathology of Addison's disease.

*High blood-pressure* is not caused by overaction of the heart, but by peripheral vaso-constriction. Almost any moderate stimulation of the body, such as cold or pain, if not excessive, may raise the pressure for a short time. Mental or bodily activity does the same. The importance of this lies in the fact that a short, and what is practically a physiological, increase of pressure may determine the rupture of a damaged artery or the final stopping of a diseased heart. The rise of arterial pressure which accompanies an increase of intracranial pressure is an ingenious attempt to force blood to the vital centres in the medulla. The same stimulation of the vaso-constrictor centre by anæmia of the medulla is of use in counteracting the immediate effect of a large hæmorrhage. With regard to the vessels themselves, high pressure leads to contraction rather than relaxation of the muscular coat. This effect lasts, however, only a short time, and is probably of little importance.

With the onset of middle age there is commonly some rise of general arterial pressure. A pressure of 130 or even 150 millimetres cannot be regarded as altogether unnatural in active persons about forty-five years old. This *hyperpiesis*, as it is called, is not to be looked upon as a primary disease or as an error of function which the body would correct if it could. It should be regarded as a compensatory precedure. For it is not credible that the vasomotor apparatus would permit such an increase to persist and steadily increase for many years unless some end were to be gained. The disadvantages of a high blood-pressure have been already indicated in considering atheroma and arterio-sclerosis. Increased work is also thrown upon the left ventricle, and those parts of the body in which the vaso-constrictor apparatus is poorly developed (brain, lungs, and to a less degree the limbs) are congested. In some instances hypertrophy of the suprarenals is found, which gives direct anatomical evidence that the body is doing its best to keep up the excessive pressure. The same conclusion is indicated by the observation that an increased arterial pressure may be kept up to the end in persons dying of cardiac failure induced by that high pressure. The change which so frequently comes on in middle life, and to which hyperpiesis is compensatory, is not clearly known.

But it may be surmised that it is the increased rigidity of the arterial walls. This acts in two ways: in the first place, it is an experimental fact of the artificial schema that, with an intermittent inflow, the outflow becomes less as, other conditions remaining the same, the rigidity of the tube increases. To get the right amount of blood through the capillaries—and this is the whole object of the circulation—it is therefore necessary to increase the driving pressure. In the second place, it seems that this increase of rigidity must entail a loss of vasomotor flexibility. The whole volume of circulating blood is normally distributed among the various organs according to their varying requirements by the exquisite adjustment of the vasomotor mechanism. If any one organ wants more blood, local vaso-dilation occurs, and there is no alteration in arterial pressure. But if the local vasomotor apparatus does not work very well, the necessary increase of supply can only be brought about by raising arterial pressure.

Hyperpiesis commonly goes with arterio-sclerosis, but it is not necessarily accompanied by any gross changes in the arteries. It is apt, however, to produce both hypermyotrophy and the intimal overgrowth in middle-sized and small vessels which is probably atheroma. Such vessels appear, when examined in the ordinary way, to have lumina of reduced size. As far as hypermyotrophy is concerned, it may be that this appearance is fallacious, and is produced by the contraction of the hypertrophied media. Assuming, however, that the lumen is in reality less than normal, we find that hyperpiesis itself produces a condition which tends to cause a further increase in blood-pressure if the capillary circulation is to be maintained. A comparatively small diminution of internal diameter much reduces the functional capacity. With the proviso that it is not altogether safe to transfer results obtained outside the body with artificial tubes to the *in vivo* behaviour of arteries, it may be stated that, if the diameter of the tube is diminished by one-tenth, the outflow with constant head of pressure falls by about a third, and the pressure required to give the same outflow is increased some three times.

There is some close connection between persistent high blood-pressure and disease of the kidneys. This is particularly marked in cases of chronic general nephritis, where, indeed, the association is so frequent that it has been supposed that arterio-sclerosis and granular kidneys are parts of the same disease. It may be that some instances of chronic general nephritis are directly caused by a diminution of blood-supply due to arterio-sclerotic changes in the renal vessels. This is, however, certainly not the general cause, and it seems likely that the etiological relation, if any, of the two conditions is in the reverse direction, in the sense that the increase of the media and intima is due to a persistent rise of blood-pressure which is compensatory to arterial rigidity and

lack of vasomotor flexibility in the renal vessels, and which aims at driving the proper quantum of blood through the kidneys. In this connection it is perhaps peculiarly instructive that a similar rise of general blood-pressure is found in cases of hydronephrosis, in which there is a general obstruction to the renal circulation and a more or less considerable diminution in the bulk of secreting tissue. On the other hand, it is open to question whether there is any causative connection at all between hyperpiesis and arterio-sclerosis on the one hand, and chronic general nephritis on the other. Both are very common as obvious diseases, and in a larval form are found still more frequently in middle-aged and elderly people. It is therefore not easy to be certain that they are more than associated conditions. It is stated that adrenal hypertrophy is decidedly more frequent in those cases of hyperpiesis which have also an advanced degree of chronic general nephritis. If this be so, it forms a fairly cogent reason in favour of the opposite view. It may, indeed, be argued that some trace at least of the anatomical changes (glomerular obliteration) which are believed to form the starting-point of chronic general nephritis may be found in a majority of adults, and that therefore it is possible to look upon all hyperpiesis as having ultimately a renal origin.

Persistent high blood-pressure occurs not only in the clinically distinct phases of chronic general nephritis which are distinguished as "contracted granular kidney" and "chronic parenchymatous nephritis," but also in the acute and subacute toxic degeneration of the secreting epithelium of the convoluted tubules which we know as "acute nephritis." In cases of idiopathic primary acute nephritis, a high blood-pressure is found to be present as soon as any other symptom, and, in a general way, to diminish and disappear as the kidney condition improves. It has been suggested that in these cases the rise of pressure is due to the production by the injured kidney of some pressor substance or to its failure to excrete some such body in a normal way. Such a supposition seems to be unnecessary. Kidneys in a condition of acute nephritis have recently been inspected *in vivo* on many occasions, and in a number of instances it has been shown that, if the state of turgid congestion in which they are found to be is relieved by incision of the capsule, they may resume a satisfactory degree of functional activity. The high blood-pressure therefore may be regarded as part of an attempt to force blood through kidneys for which local vaso-dilation can obviously do little or nothing.

No case, therefore, of persistent high blood-pressure is known to be directly due to a primary over-production of pressor substances by the suprarenal or pituitary bodies. Substances which are potent to raise blood-pressure are also developed by bacterial action in the bowels, and may be excreted in the urine in traces. Parahydroxyphenylethylamine gets into the body in this way.

It has been suggested that, when there is excessive or abnormal putrefaction in the intestine, this substance may be absorbed in quantities sufficient to account for much of the persistent high blood-pressure considered above. Quantitative experiments show, however, that the amount required to do this is much more than can reasonably be supposed to be derived from the intestines.*

**Local Vasomotor Phenomena.**—The pathology of the vasomotor apparatus regarded as the means whereby the distribution of blood is controlled requires further mention. The flushing of an inflamed area is an example of a local vaso-dilation. More blood is wanted to render the irritant innocuous, to assist reparative cell growth, and, on the surface of the body, to raise the temperature. This is obtained by local vaso-dilation in the same way as the stomach obtains more blood when it wants to digest a meal. Frost-bite is caused by an immoderate local vaso-constriction due to cold. In some persons a cold bath produces a general cutaneous cyanosis. The effect is, however, greatest in the extremities, and is often confined to them. The arterioles are firmly constricted, and the blood remains stagnant in the capillaries and veins, because there is nothing to push it on. In these common cases the arterial supply is seldom cut off for long enough to cause appreciable tissue destruction. But in *Raynaud's disease* we have a spasmodic intense local vaso-constriction, mostly in the arms and legs, but with apparently analogous states in the viscera, which may result in necrosis of the part supplied. An attack is often precipitated by exposure to cold. At first the fingers, for example, are anæmic and cold. As the constriction passes off, an active congestion occurs, and the part is more than usually full of freely-circulating blood and somewhat œdematous. This is the usual reaction when blood re-enters an area which has been anæmic. The part may also sometimes be swollen, congested and cyanotic, a combination which seems best explained by a spasm of the veins. The arteries may be much narrowed by endarteritis. This accentuates the effects of vaso-constriction. Erythromelalgia, or one of the conditions included under that name, is probably essentially a local vaso-motor paralysis.

**The Circulation in Veins.**—The veins normally contain much less blood than their total capacity would easily allow. They are in large part passive and rather uninteresting channels which secure the return of blood to the heart, and which are prepared to transmit (within reasonable limits) all the blood which reaches them.

The motive force of the venous circulation is essentially the left ventricle. There are also certain accessory mechanisms which are of considerable importance. The negative intrathoracic and intra-cardiac pressures during inspiration and diastole are powerful

* Clark, *Bioch. Journ.*, 1910, vol. v., p. 236.

agents in drawing the contents of the great veins into the heart, and hence encouraging the venous flow in general. These factors only come in operation if the supply of blood to fill the veins from the distal end is abundant. A negative pressure within veins cannot be other than slight in degree and brief in duration without the lumen of the vessel being obliterated by atmospheric pressure. Hence free and full respiration promotes the return of blood to the heart, and anything which impedes respiration—obstruction in the air-passages, the pain of acute pleurisy, the filling up the pleura with fluid — hinders the circulation. Conversely, an abnormal increase of intrathoracic pressure obstructs the venous return. Efforts at expiration with a closed glottis, either in the academic cough known as "Valsalva's experiment" or in the ordinary procedure, may practically prevent any blood getting into the right heart at all. The engorged veins may be seen on the surface of the body, and felt inside the head, while the arterial circulation fails. The other important accessory factor is muscular movement, including the respiratory movements of the abdomen. Everyone is familiar with the venous engorgement and uncomfortable feeling of fulness and tension which can be produced by allowing an arm or a leg to hang vertically for a short time with as little action of the muscles as possible. To be effective in pumping the blood along the veins, muscular movement should be interrupted rather than continuous. In this way use is made of the valves, which support the blood pressed towards the heart by one muscular contraction while the vessels are filling again from the periphery during the period of muscular relaxation. If no intermittent muscular movements are made while the body is in the erect position, the venous blood gets back to the heart so badly that the output from the left ventricle may not be sufficient to keep the brain well supplied. Hence soldiers faint after standing still for some time. "Marking time" prevents this anomaly.

In thinking of the venous circulation, it must be clearly recognized that it only forms part of the circle from left to right ventricles. After death all the blood in the body may pass into the veins, but during life a process of accumulation in the veins cannot go on for very long, unless the total volume of circulating blood is continually increasing. In conditions where a partial failure of the pumping action of the heart brings about an obvious turgidity of the veins, the total quantity of blood may or may not be increased. But such an increase of venous fulness cannot go on indefinitely. Hence long-continued overfilling of the veins commonly indicates an abnormally slow rate of arterial and—which is the important thing—capillary circulation. If there is an impediment to the exit of blood from the veins, it is clearly impossible for blood to continue to enter them through the capillaries at the normal rate for an indefinite period. The ill effects on the liver and other organs are not due to the

increased venous pressure (for such does not exist), but to malnutrition due to a sluggish blood-flow, which kills the proper parenchyma, and may lead to a compensatory increase in fibrous tissue. It is a matter of common observation that the engorged veins of cardiac disease may yield very little blood when they are opened. The improvement of cardiac efficiency which often follows the abstraction of blood in these cases is rather remarkable. If, however, we regard inspiration as the chief factor which regulates the filling of the right heart, it is not difficult to see how the heart may be overfilled and embarrassed in its action if the available blood is over-abundant, and the cardiac muscle is not at its best.

Local obstruction of veins generally arises by the vessel being blocked by a thrombus from within, or pressed upon by a tumour of some kind from without. Much the same result is reached if the valves become incompetent, as in the ordinary varicose veins of the leg. The lack of efficient valves allows the blood to ebb and flow in the vein without necessarily making much progress, the main return of blood passing by other channels. The partial venous stasis so produced obstructs the adequate supply of blood to the parts immediately adjacent, and malnutrition is shown by the alteration in the growth of the skin and its accessory structures, as well as by the liability to necrosis. Owing to the extreme freedom of the collateral circulation, blocking of veins causes actual death of the parts involved even less frequently than does arterial obstruction. If, however, the venous return from any tissue is mostly stopped, or if the tissue is particularly liable to death from anæmia, the supply of arterial blood becomes insufficient, and the results are just the same as if the primary fault had been in the arteries. Thus, venous thrombosis in the intestines, the liver, the kidneys or the brain, may lead to death of large masses of tissue. More commonly the venous return is only partially obstructed, as in thrombosis of the femoral or other large vein, or in the general obstruction produced by cardiac disease or increase of intrathoracic pressure. The tissues then do not die suddenly *en masse*, but are slowly killed off piecemeal, as in a "nutmeg" liver.

## Œdema.

Œdema signifies the unnatural accumulation of fluid more or less resembling lymph in the tissues and serous sacs. The condition may be quite localized, or practically universal throughout the body. It is known mainly as a phenomenon occurring in connection with inflammation, renal disease, disordered circulation of blood or lymph, anæmia and certain nervous states. While the amount of water in the body may vary a good deal from time to time, the volume of the circulating blood tends to remain remarkably constant under a variety of different circumstances. This is effected by using the

tissues as a place of storage when there is more water in the body than is necessary, from which water may be brought into the blood when wanted. If, for example, blood be injected into the circulation, the plasma is soon thrown out of the bloodvessels. It is not necessarily excreted by the kidneys for a long time afterwards, but may remain in the tissues. But this method of adjustment covers only small amounts of water and short periods of times, and does not bring about a condition in which an obvious excess of liquid in the tissues may be detected *in vivo*. It is apparent that there may be much too much water in the tissues without any alteration in the contour or consistence of the parts of the body which can be examined in an intact man. By the term *œdema* in human pathology we mean the accumulation of a considerable and obvious excess of tissue fluid.

The lymphatics form a closed system of vessels, ending in the great veins near the heart and ramifying throughout the tissues. This system communicates directly with the peritoneal cavity, though the communications are in man and many animals small, often apparently absent and of doubtful functional significance. At their distal end the lymphatic vessels have no direct communication with, but are separated by a layer of endothelium from, the " tissue spaces "—those intervals between the perceptible structural elements which disease or post-mortem changes may magnify into obvious lacunæ. The liquid in these spaces is the medium which is in direct relation with the tissue cells, and is outside both bloodvessels and lymphatics. It may be called " tissue fluid." The larger lymphatic trunks appear to anastomose to some extent with the neighbouring venules.

The *raison d'être* of the lymphatic system is obscure. The fluid within it is doubtless derived from the blood-plasma, and it thus provides a route for the return to the heart of liquid which has passed out of the bloodvessels to carry food to, and remove waste products from, the tissues. But this route is only an alternative to that provided by the veins. Experiments have shown that there is no particular difficulty in fluids in the tissue spaces and in the peritoneum being absorbed into the bloodvessels. Thus dyes and poisons injected into the tissues or serous sacs may be demonstrated to pass to other parts of the body by the blood-stream, as well as by the lymphatics. The evidence, however, is not so clear that such absorption takes place under completely normal circumstances of distribution and composition of fluids within and outside the vessels. It is obviously not possible to identify liquid, which has left the bloodvessels to form tissue fluid, with sufficient accuracy to say whether it passes from the tissues back to the bloodvessels by the lymphatics, or is directly reabsorbed into the venous side of the capillaries. It has, however, been found that the blandest fluids may quickly disappear from the peritoneal cavity without

any appreciable increase in the lymph flow in the thoracic duct. On the whole there seem to be no conclusive reasons for doubting that some tissue fluid is normally reabsorbed into the veins, while some is returned to the blood by the lymphatics. There is no obvious reason why the veins, which in this connection can only be regarded as indifferent channels, should be avoided by tissue fluid in general as a means of return to the heart, though in absorption from the alimentary canal special considerations may render such a course desirable. Assuming, then, that tissue fluid can under normal conditions return to the heart by the veins, we must conclude that there are special reasons why it should return by the lymphatics. What these are can only be surmised. It may well be that tissue fluid is, after intimate contact with living cells, in some way unsuitable for immediate distribution to other cells, and that it is necessary either to purify it from the products of tissue metabolism or to add to it substances in which it is now deficient. The anatomy of the parts suggests that the accumulations of lymphoid cells lying along the paths of the lymphatic vessels do something to the lymph. We have, however, no definite knowledge on this point. If we assume that only a part of the tissue fluid returns from the tissues by the lymphatics, and that the object of the lymphatic apparatus is to remove or modify toxic substances derived from tissue metabolism, we must also assume that there is a differential absorption of these substances from the tissue spaces by the endothelium of the lymphatics and by that of the venous capillaries. It is possible, for example, that a larger proportion of tissue fluid is absorbed into the veins when the tissues are resting than when they are active. It is only under conditions of activity that much fluid passes away from a part by the large lymphatic trunks. Such an assumption introduces more, but not necessarily unnatural, complications. These to some extent disappear if we regard the lymph as tissue fluid passing along a sort of by-pass, where it may collect something which is desirable, before, by its slow and circuitous path, it is returned to the blood to "make it more subtle and enliven it."

The composition of lymph is qualitatively much the same as that of blood-plasma. Quantitatively it differs chiefly in containing less protein, though the relative proportions of the other constituents, including the salts, are not quite the same as in plasma. Lymph from different parts of the body varies in composition. Thus liver lymph contains about three times more solids than lymph from the leg. The total osmotic pressure of lymph bears a variable relation to that of the blood-plasma from which it is derived. It may be more, the same, or less. These facts apply to lymph found flowing along the larger lymphatic vessels. We do not know the composition of lymph at its seat of formation, still less that of tissue fluid.

It will be obvious that the problems connected with the normal and abnormal formation of lymph are of considerable complexity, and present great difficulties in the way of experimental investigation. In any case we have to take into consideration (1) the passage of fluid through the endothelium of the blood-capillaries into the tissues; (2) the retention of this as tissue fluid; (3) the absorption of tissue fluid, more or less altered by contact with the tissues through the endothelium of (*a*) blood-capillaries, or (*b*) lymph-capillaries; and (4) the passage of this lymph along the lymphatics. Quantitative data as to these different items are difficult to obtain. They chiefly consist in observations of the quantity of lymph passing along the larger lymphatics and of the amount retained as tissue fluid. This latter can be estimated only roughly. In human pathology direct observation only tells us of the presence or absence of such a large excess of tissue fluid as causes obvious œdema. For the rest we have to rely on indirect evidence obtained from the body weight, the composition of the excretions, and the volume of the limbs and other accessible parts. For purposes of discussion, it is customary to assume that tissue fluid is always absorbed in the same proportions by the bloodvessels and the lymphatics, and that the amount of lymph leaving any part of the body is an approximately accurate measure of the quantity of fluid leaving the bloodvessels, unless the onset of perceptible œdema, or some alteration in the composition—*e.g.*, the specific gravity—of the tissues, indicates a retention of tissue fluid *in situ*.

The main fact of outstanding importance which has been ascertained in connection with the study of physiological variations in the amount of lymph leaving any part of the body is the correlation of lymph flow with specific functional activity. Very little lymph flows away from a limb at rest or from a resting pancreas. Muscular activity in the one case and the secretion of pancreatic juice in the other are associated with an immediate and manifold flow. In the same way the administration of substances, such as bile salts, which excite the liver to greater activity in bile production causes a parallel increase of lymph flowing along the thoracic duct, which from its high content in proteids may be identified as being liver lymph. Such states of specific functional activity are well known to be accompanied by a great increase in local blood-flow, and it is an obvious inference to connect with this the increase of lymph. The salivary glands, however, furnish a special case which shows that such an inference is not in all cases permissible. Stimulation of the chorda tympani is followed by increased blood-flow, increased production of saliva, and increased lymph flow. After the administration of atropin, however, stimulation of the same nerve, while bringing about the same vaso-dilation, causes a flow neither of saliva nor of lymph. These facts are concordant with the *a priori* notion that the lymph flow exists for the benefit of the tissues,

and lead us to look to the tissues for the factors which are dominant in regulating the variations in the amount of lymph rather than to the blood and bloodvessels.

At the same time experimental investigations of the influence of the circulation on lymph production have furnished many suggestive facts. Alterations of the circulation which in one way or another bring about an increase of intracapillary pressure are associated with an increase of lymph flow. This is so whether the rise of capillary pressure is brought about by a general and sudden increase in the volume of the blood (as by injecting large quantities of salt solution directly into the circulation, or by injecting concentrated solutions of, *e.g.*, dextrose, which abstract water from the tissues), by a local active hyperæmia produced by warmth or other means, or by venous obstruction. One may also lay it down as a general rule that a rise of arterial pressure tends to be followed by a concentration of the blood, which must mean that fluid passes from the blood to the tissues, and, conversely, that when the arterial pressure falls (providing it be from vasomotor influences which do not materially affect the venous pressure) fluid is taken up from the tissues by the blood, which becomes more dilute. It is also known that a rise of intracapillary pressure is somewhat more effective in promoting a flow of lymph, if at the same time the composition of the blood has been varied in the direction of hydræmia.

Before, however, these and kindred observations are transferred to the phenomena of normal lymph flow—still more, perhaps, before they are transferred to the facts of œdema in human pathology—it is necessary to realize that the alterations in the circulation produced by these experiments are for the most part of sudden onset, short duration, and extreme degree; and instead of thinking that the changes merely exaggerate the natural phenomena of health and disease, which is, of course, almost an experimental necessity, it may be more correct to hold that they are of such a character that they differ qualitatively rather than quantitatively from those which are in operation in the body when left to itself. It may be, in short, that such procedures as ligation of the inferior vena cava, or increasing the content of the circulatory system two or three fold, do not open the ordinary doors a little wider, but force altogether fresh channels by an exhibition of force which the structures concerned cannot be expected to stand at such short notice.

Tissue activity involves the necessity of more food coming out of the blood for the use of the active cells. It is therefore reasonable to think that the increased flow along the lymphatics which accompanies tissue activity is the result of an actual increase in the amount of fluid leaving the blood, though the possibility cannot be excluded that it is, at any rate in part, due to a redistribution of tissue fluid between the venules and lymphatics. The mechanism by

which the increase is brought about is not clear, and it is doubtful whether it can be described more definitely than as an act of secretion by the endothelium. Tissue activity is associated with an increase of katabolic over anabolic changes. The result is that the tissue is at the end of a period of activity constituted, on the whole, of simpler compounds, and has a higher osmotic pressure than at the beginning. The increased water-attracting power of active tissues has been demonstrated by direct experiment, and suggests an explanation of how more water leaves the vessels in states of activity. But it suggests no reason why the tissue fluid is subsequently passed on either into the veins or into the lymphatics. It furnishes, indeed, definite reasons why it should accumulate in the tissues. As has been already mentioned, direct examination of lymph shows that it may have an osmotic pressure higher or lower than that of the blood-plasma.

There are certain phenomena which suggest that the endothelia, either of the blood or lymph capillaries or of both, are under a nervous control which can modify the amount of liquid passing through them. The production of local œdema by hypnotic suggestion, dermographia (where a localized œdema is produced by a slight mechanical stimulus), and the morbid condition known as "angio-neurotic œdema" (where œdema of an intense but fleeting character involves a part of the body), all support such an idea, though whether the whole nervous influence is exerted on the capillary walls to the exclusion of the extravascular tissues has not been ascertained.

Of variations in the flow of lymph in natural pathology practically nothing is known. Consideration must be confined to states in which lymph accumulates in the tissues—in which, that is, œdema is present. Such an accumulation might be produced by excessive formation, deficient removal, or both factors combined. It is only rarely that we have any idea as to which, if either, is the predominant factor. It is commonly considered that excessive formation of tissue fluid is usually a condition of the production of œdema. It is, however, clear that œdema is by no means the necessary consequence of such excess. Considering the ease with which the exaggerated lymph flow in tissue activity is disposed of without any undue accumulation in the tissues, it would seem probable that the fundamental factors in œdema concern the removal of tissue fluid through the endothelial wall of the lymphatics rather than its formation from the blood-plasma. The circumstances, indeed, which are known to increase the flow of lymph along the lymphatic trunks may operate just as well in the direction of preventing as towards causing œdema.

Of the different conditions included under the term "œdema" in human pathology, *œdema a vacuo* is the simplest. It is seen especially in connection with the central nervous system. If the

proper tissues shrink in volume, as in atrophy of the brain, or if the fat within the spinal canal wastes, a potential space is left. The rigidity of the skull or vertebræ prevents the surrounding tissues falling in to fill up the gap, which therefore becomes occupied with the only available material—*i.e.*, lymph or tissue fluid. The same happens if the air is exhausted over a localized area of skin. The bloodvessels bulge as much as they can; but if this is not enough, plasma exudes out of them into the tissues.

**Œdema in Lymphatic Obstruction.**—Blocking of the large lymphatic trunks is always liable to produce œdema, though, owing to the freedom of the collateral circulation, this does not necessarily ensue. The condition is most often caused on a large scale by the obstruction due to the nematode *Filaria*. The occurrence of œdema of this type is of general interest, as it seems to show that all the tissue fluid cannot always be returned by the veins. At the same time it is possible that lymphatic, like venous, obstruction impairs the nutrition of the tissues, and the accumulation of tissue fluid may be due to this factor rather than to any direct mechanical effect.

**Œdema of Inflammation.**—The essential phenomena of the inflammatory process concern the tissues, and the vascular changes are subsidiary and directed towards the more perfect accomplishment by the tissues of the due sequence of their activities. The outpouring of plasma is of use in the first place to dilute the irritant (whether this be the primary cause of the inflammation or the secondary irritant produced by autolytic processes in the injured cells), whereby its destructive effect may be diminished, and perhaps even converted into a stimulus to increased tissue activity; in the second place to carry more food to the surviving cells, whereby they may more quickly discharge their reparative functions; and in the third place to bring to bear upon both the irritant and the cells engaged in defence those protective substances which are normally concentrated in the blood. Though we thus understand more or less why inflammation is accompanied by œdema, the question of the immediate mechanism of its production is obscure. We have at least three factors which have to be considered—the deliberate secretory activities of the endothelium of the blood and lymph vessels; the alteration in the endothelium of the blood capillaries, which is often so considerable as to allow the escape of red cells; and the presence outside the vessel of the products of disintegration of the sick and dead tissue cells and leucocytes.

**Œdema in Venous Obstruction: Cardiac Œdema.**—Venous obstruction may be followed by œdema to a greater or less degree. Such obstruction may be produced by the ligature of large venous trunks or by the pressure of malignant and other tumours. Of more

frequent occurrence is the œdema which is seen in association with the general venous obstruction produced by cardiac or pulmonary disease. Venous obstruction, if quantitatively and topographically adequate to produce a rise of venous pressure, entails a corresponding rise in intracapillary pressure. A direct cause of the appearance of œdema in such cases is at once suggested. There are, however, a number of facts which indicate that such an explanation is inadequate. Experimental ligature of a large venous trunk —*e.g.*, the femoral vein—is not followed by œdema for many hours. If, however, the limb has been previously rendered abnormal by being kept either empty of blood or full of stagnant blood for an hour, a comparatively small rise of venous pressure soon produces a marked degree of œdema. This experiment suggests that it is not the venous obstruction *per se* which causes the œdema, but the changes in the capillary walls or in the tissues which are induced by imperfect nutrition brought about by venous obstruction, anæmia of the limb or hæmostasis by a general ligature round the whole number. It must, indeed, be recognized that œdema of a part may follow ligation of the artery supplying the area in question. Cardiac œdema is difficult to reproduce experimentally, since in nature it follows changes of slow development the consequences of which are constantly subject to compensatory phenomena. A study, however, of the mechanism of the production of the œdema following experimental cardiac embarrassment or partial obstruction of the great veins lends no support to the view that increased capillary blood-pressure is the determinative factor. By reducing the capacity of the pericardial sac the intake and output of the heart are diminished, venous and capillary pressures rise, and arterial pressure falls. But these changes are only temporary; within a few hours compensation is effected, and the pressures in the various parts of the circulatory apparatus are found to be distributed in a normal manner. Yet in a few days considerable œdema is produced, and that under circumstances which preclude the possibility of an increased intracapillary pressure. So, in the case of œdema occurring when the circulation fails from cardiac disease in man, the blood is evidently stagnating in the veins, but of the existence of a definite increase in venous pressure there is no clear evidence, and arterial pressure is known to be generally not less than normal or thereby. As in local venous obstruction, œdema in these cases seems to depend upon the changes produced in the capillary wall or the tissues by imperfect circulation. It is hardly likely that such changes in the capillary walls can at present be expressed in terms of histological structure. We may be able to judge of their existence only by studying the amount of fluid which they allow to leave the vessels. We have, however, no reason for concluding definitely that any change produced in the endothelium by defective nutrition must necessarily operate in

the direction of allowing more fluid than normal to escape. It is the business of the endothelium to pass fluid from and to the blood and tissues, and it is not unreasonable to suppose that any impairment of its general well-being would depress its specific functional capacities in every way. It is, moreover, clear that, if the blood-capillaries allow more fluid to pass to the tissues, the endothelium of the lymphatic capillaries should also allow more to pass away from the tissues. In any case, the hypothesis that cardiac œdema depends on alterations in the capillary wall fails to explain why the excess of fluid is not removed from the tissues, unless the alteration affects the passage of fluid from the blood to the tissue spaces in a different way to that from the tissue spaces back into the veins and lymphatics. This may be so, and it should be remembered that, as far as definite evidence is concerned, the hypothesis that in cardiac œdema the lymphatic or vascular endothelia fail to secrete enough tissue fluid into the lymphatics or veins, as the case may be, is as probable and as incapable of demonstration as that which suggests that, under like conditions of starvation, the endothelium of the bloodvessels passes too much fluid out into the tissues. The fact, indeed, of cardiac œdema is that fluid is retained in the tissues, not, as far as our knowledge goes, that more leaves the bloodvessels or less passes along the lymphatics, probable as these assumptions may at first sight seem to be. There is therefore some justification for considering that cardiac œdema depends upon the changes which are brought about in the extravascular tissues by an inadequate circulation. We should expect an attempt on the part of the tissues to compensate for a diminution of the supply of oxygen by bringing about an increased flow of fluid from the blood; but here again we meet the difficulty of accounting for the imperfect removal of that fluid, and on this hypothesis the presence of a considerable œdema would largely defeat its own ends. An undue accumulation of metabolic products in the tissue fluid would provide a fairly satisfactory explanation of the observed phenomena, and such evidence as we possess does not negative the assumption that the osmotic pressure of this fluid is maintained at an unnaturally high level in cases of cardiac œdema. Such an hypothesis would, at any rate, afford some reason for both an excessive loss of fluid from the blood and a deficient absorption into the lymphatics. There is evidence that injury to cells (such as is caused to the liver parenchyma by the injection of peptone) leads to an increase in the amount of lymph leaving the part.

Cardiac œdema is commonly distributed about the body in accordance with the effect of gravity, being most marked in the more dependent parts. The theory of tissue starvation affords an explanation of this fact equally with the theory of increased intracapillary pressure, since the circulation will attain its maximum of

inefficiency in those parts where the influence of gravity comes prominently into play.

The possibility should be mentioned that cardiac œdema has its genesis in the detrimental effects of a bad circulation on the kidney (and perhaps other organs), and should therefore be regarded as a form of renal œdema. Such a notion is primarily objectionable because it cannot include the œdema of local venous obstruction.

**Œdema of Anæmia and Cachexia.**—Œdema may accompany any form of anæmia, but is not constantly present in any. It occurs both in chlorosis, where a condition of true hydræmic plethora exists, and in pernicious anæmia or anæmia from hæmorrhage, where there is a real deficiency of hæmoglobin. The factor common to all anæmias is the diminution of the oxygen-carrying power of the blood per unit volume, and the tissues in all varieties suffer a greater or less degree of chronic starvation. The same condition may occur in the cachectic states produced by, *e.g.*, phthisis or malignant disease, though here the defect in assimilation arises in quite a different way. The distribution of anæmic œdema follows gravity as in cardiac œdema, and its explanation, whatever that may be, is no doubt much the same. The underlying feature is in all cases imperfect tissue nutrition, and that this similarity obtains under circumstances where the circulatory conditions are so widely different points again to the tissues rather than the vessels as the source of the œdema of anæmia as well as that of venous obstruction.

**Renal Œdema.**—Obvious œdema is very frequent in acute degeneration of the secretory epithelium of the kidney (whether this be an "acute primary nephritis" of unknown cause or due to such poisons as chrome salts or corrosive sublimate), in the nephritis associated with scarlet fever, and in that form of chronic general nephritis which presents the symptom-complex of "chronic parenchymatous nephritis." On the other hand, it is rarely, if ever, found in the disease known as "chronic interstitial nephritis," in destruction of kidney substance by inflammation or tumours, or in obstruction of the urinary outflow. The onset may be very sudden, and widespread visible œdema may be the earliest symptom of acute nephritis. The distribution differs from that seen in cardiac cases, being determined more by the laxity of the tissues than by the influence of gravity. From this we may conclude that the cause of renal œdema, whatever it may be, affects the whole body equally, and the fluid first accumulates where there is most room for it. With a failing circulation, on the other hand, the cause of the œdema is localized, and it is most marked where the circulation is, by the effect of gravity, at its worst. While this distinction holds good in most cases, it should be mentioned that the study of the early stages of experimental œdema of circulatory origin

suggests that here also mechanical conditions play a large part in determining the place in which extravascular fluid first begins to accumulate.

The explanation of renal œdema is not known. Considering the various factors which may be of importance, we note in the first place that the whole body, including the apparatus which presides over the distribution of tissue fluid, is evidently more or less under the influence of some toxic substance; the symptoms presented are more than can be accounted for by the mechanical inconveniences of œdema. The circulatory conditions may also be abnormal; arterial blood-pressure is nearly always considerably raised, and in many cases of renal disease, both with and without œdema, the blood is diluted and an hydræmic plethora exists. It seems obvious enough at first sight that, if no urine or a much-diminished quantity of urine is excreted, water must accumulate in the body, and that it is natural that this excess of water should accumulate in the tissue spaces rather than in the circulating blood. Persons may, however, die because their kidneys cannot do enough work (chronic general nephritis, cystic kidney, blocking of both ureters), without showing any signs of œdema. It is difficult, therefore, to believe that the retention of water or any of the other constituents of normal urine within the body is the effective cause of renal œdema. On the other hand, the facts show no more than that œdema is not the invariable result of such retention; and just as the cerebral or respiratory symptoms of persons suffering from the more severe grades of renal inadequacy vary a great deal from case to case, so it may be that the tissue-fluid symptoms are inconstant.

Recent investigation has shown a notable relation between the excretion of salt and the presence of œdema. The excretion of chlorides is diminished in nephritis, and the experimental administration of salt by the mouth shows that it is excreted much less readily than in health. In such persons it has been found possible to bring on, increase or diminish œdema by increasing or diminishing the intake of salt in the food. Even in normal persons there are grounds for believing that the amount of tissue fluid, and to a less extent the concentration of the blood, varies with the amount of salt taken. In cases of nephritis such a relation presents two possibilities: either retention of water is primary, and the chlorides are not excreted because they are wanted to keep up the salt content of the body fluids to the normal level; or retention of salt is primary, and water is detained to prevent an undue concentration of tissue fluid. There are a number of data which indicate, though not conclusively, that the latter alternative is probably to be preferred. Thus, the inability of the kidneys to secrete salt is independent of their activity as regards other substances (phosphate, urea, methylene blue, etc.), and during the course of a declining

œdema the increased excretion of salt has been observed to exceed that of water. The concentration of salt in the body fluids in cases of œdema is on the whole somewhat higher than normal; the difference is, however, small and inconstant, as one would indeed expect on either hypothesis. The facts as a whole, however, seem capable of a different interpretation altogether. Putting aside any question of the functional capacity of the kidneys, it may be supposed that the actual amount of salt excreted is determined by the tissues. If the tissues want to have more fluid in them, they require water and salt. If either fails, there will be no fluid available suitable for their purpose, and no œdema will ensue. If more salt is given them, they will retain it as long as possible and become more œdematous; if salt is excluded from the diet, they will have to slowly use up their accumulation to adjust the concentration of the urine, the salt content of the œdema fluid will tend to fall, and hence water will also leave the tissues and they will become less œdematous. On this interpretation the apparent inability of the kidneys to excrete salt would be due to the avidity with which salt is desired by the tissues, and the immediate cause of renal œdema would be removed from the kidneys to the tissues. To some extent this view is supported by the observation that a similar relation between intake of salt and œdema obtains in some cases of cardiac œdema. As has been already indicated, it is possible that cardiac œdema is due to renal inadequacy caused by an imperfect circulation. The balance of evidence is, however, against this hypothesis, and it is easy to understand how cardiac œdema may be diminished by a salt-free diet, and how the kidneys in such cases may excrete salt less freely than normal, without supposing that there is a primary renal inability to put salt into the urine.

That œdema has some special relation with kidney function seems clear. There is, however, an obvious lack of correlation between œdema and the excretion of urine, which suggests the possibility that the other activities of the kidney ought to be taken into account. It should also be noted that it is an assumption to conclude that the œdema is necessarily a result of the renal disease. In point of time œdema may be the earliest observed abnormality, which is the more striking when we consider that there may be considerable accumulation of tissue fluid without any obvious œdema. It may be, then, that the œdema and the renal disease have a common cause, and are not dependent one on another. The causes of the ordinary forms of nephritis which are associated with œdema are quite unknown.

## CHAPTER X

# THE NERVOUS SYSTEM

By F. W. MOTT and S. V. SEWELL

**Introduction.**—Our present knowledge of the nervous system and of the diseases to which it is liable has been obtained from a proper appreciation of the neurone in its relation to neuropathology.

A new era in the study of the nervous system may be said to have commenced in 1850, when Waller published his communication "Experiments on the Section of the Glossopharyngeal and Hypoglossal Nerves of the Frog, and Observations of the Alterations produced thereby in the Structure of their Primitive Fibres." Waller then proved that a change took place throughout the whole of the nerve below the point of section, and extended to its terminal points. In 1852 Türck described secondary degeneration of the spinal cord after a transverse lesion, and in 1854 published a paper on secondary degenerations of tracts in the spinal cord and their prolongations in the brain. To the work of Waller we owe the foundation of our knowledge of secondary (Wallerian) degeneration of the peripheral nervous system, and to Türck the foundation of our knowledge of the central nervous system. From their work, continued and elaborated by numerous other observers, we have derived our present conception of the neurone doctrine formulated by Waller, revived by Forel, and reintroduced by Waldeyer in the following terms: "A neurone is a nerve cell with all its processes or dendrons, and the single axis cylinder process with its cone of origin, its collaterals or side branches, and its terminal arborization." The *neurone theory* is that the nervous system consists of innumerable such anatomically independent nervous units in contiguity, but not in continuity. There is interlacing of the processes, but no network. The nervous units are genetically and trophically independent cellular organisms.

In the embryonic state the nervous system consists of cells; like other organs, each cell is confined within microscopic limits, but the inherent specific energy of each neuroblast is manifested by a tropism, a chemical or physical attraction by which extensions of the cell occur, one to form the axon, the other the dendrons. These

tropisms have been built up in the process of evolution and adaptation to environment, so that there is an inherent affinity between a sensory neurone and its peripheral receptor, a motor neurone and its effector, and between these and the appropriate association neurones. The older phylogenetically and ontogenetically these tropisms, the more fixed and stable are they. The neurones form functionally correlated systems, groups, and communities of increasing numbers and complexity as we rise in the animal series.

According to the law of dynamic polarization, every neurone receives stimuli, either on the surface of its cell body or on that of the dendrites; the axon is reserved exclusively for the discharge of stimuli, which are liberated either on the cell bodies or dendrites of other neurones, or in motor organs or secreting glands. The orientation of the fibres offers, therefore, a certain indication of the direction constantly taken by the current, which is from the cell towards the terminal arborization of the axon.

Unlike other cells of the body, the neurone is a perpetual cell, and incapable of regeneration in the higher vertebrates. All the neurones are present at birth, arranged in systems, groups, and communities, each with a specific energy and durability determined by ancestral inheritance, awaiting the stimuli for their functional development. The truth of this is obvious from everyday experience, but that inherent specific energy is the determining factor in the durability of the neurone is shown by the fact that in certain familial diseases of the nervous system a premature decay and loss of function of correlated systems of neurones occur at a particular age, in a number of members of a stock in several, and sometimes successive, generations. We may seek an explanation of this in a failure of the germinal determinants of the nervous system. But the life and functions of the neurone and neuro-tropism are presided over by the nucleus; it may therefore be assumed that a failure of biotonic nutritional equilibrium may be due to a lack of some biochemical or biophysical condition of the nucleus. When we consider the extraordinary inherent potentiality of the nuclear matter of the male and female gametes—reduced germ substance—it is conceivable that the nuclear substance of the neurone possesses a potentiality whereby each functionally differentiated system of neurones inherits specific bio-rhythmical properties, enabling it to react physically and chemically to particular modes of motion caused by specific biological stimuli, essential for the preservation of the individual and the species. A bio-rhythm affecting widely-separated groups of functionally correlated neurones and the liberation of nervous energy in the reaction to stimulus would not depend, therefore, so much upon its strength as upon its biological usefulness. Again, the existence of two different types of neurone, as shown by Golgi, indicates a difference of function. In Type I. the axon leaves the grey matter to proceed

to a distant structure ; in Type II. the axon does not leave the grey matter. According to Von Monakow, the neurones of the second type, or *Schaltzellen*, are always interposed between the terminals of the axons of one neurone of the first type and the dendrites of another of the first type. The neurones of the first type are destined to discharge functional energy, elaborated in the cells of the grey matter or in a peripheral structure, *e.g.*, muscle, gland. The small neurones of the second type of Golgi are for the elaboration, local distribution, and discharge of energy ; indeed, Cajal maintains that the action is of a reinforcing nature ; they would thus be accumulators and condensers of energy, and not only would they serve to increase the discharge of stimuli, but also to lengthen the discharge. It is not surprising, therefore, that the neurones of the second type of Golgi are found in great abundance in the sensory receptor and perceptor centres of the cortex and the cerebellum. There is no essential difference in the structure of the neurones, but there are many different types of neurones peculiar to the functionally different structures ; indeed, a comparative histological examination of the cortex in the animal series exhibits differences and similarities in types of neurones and the arrangement of the layers in accordance with similarities and differences in function and modes of adaptation to environment. It is possible that each different type with a different function may consist of specific neurobions with a specific biorhythm.

All neurones consist of a nucleus surrounded by a cytoplasm with branching processes. If examined in the living state, we find a profound difference in the conception of its structure to that obtained by a microscopic examination of sections of nervous tissue after fixation and staining. Neither neuro-fibrils nor Nissl granules can be seen in the living cell, and, in the opinion of many authorities, these appearances are due to death changes, and should be regarded as artifacts. No one, however, will deny the great practical outcome of the methods employed for showing these structures in the study of the normal and pathological anatomy of the nervous system ; also of the physiological functions of the nervous system in respect to morphological co-ordination and the morphological changes occurring in degeneration, whether due to poisons, disease, or injury, and the processes of regeneration. The conception of the neurone with fibrils and Nissl bodies does not, however, explain satisfactorily the biophysical and biochemical conditions that really occur during life in the constituent colloidal substances of the neurone, incidental to its functional activity and interaction with the circumambient medium occasioned by particular modes of motion, acting as stimuli in vital action and reaction. These are biophysical and biochemical changes connected with surface tension, osmotic pressure, and movements of ions. Examination of the living nerve cell of cold-blooded animals in

serum at the ordinary temperature of the air, or of warm-blooded animals at the temperature of their body, shows neither Nissl granules nor fibrils. The neurone consists of colloidal, semi-fluid, viscid substances. The appearances presented by nerve cells when examined with the ultra-microscope give one an entirely different conception of the structure to that obtained by the examination of fixed and stained sections. The cells on the dark ground appear luminous, but the degree of luminosity varies in different cells, and in the same cell at different times. This luminosity is due to the existence of minute spherules of a colloidal fluid, which permeate the whole cytoplasm. The nucleus and nuclear membrane are distinctly seen owing to a different refractile property of the constituent colloids. If water or ½ per cent. solution of ammonia be run under the coverglass, endosmosis occurs, the water seems to act upon the spongioplasm of the cell, and the refractile spherules escape. They do not run together, and it appears as if each possessed a surface membrane; they exhibit marked Brownian movements in the surrounding fluid. The cell membrane and the nuclear membrane seem to resist the action of the water; the homogenous spongioplasm of the cell appears to absorb the water.

## Normal Structure and Functions.

**Morphology.**—The histological elements which constitute the nervous system are derived developmentally from the two outer layers of the blastoderm. From the epiblast are derived the essential nervous elements, together with the supporting neuroglial tissue, the lining cells of the ventricles of the brain, and the central canal of the spinal cord. On the other hand, the mesoblast gives rise to the bloodvessels, lymphatics, and membranes of the brain. The neurilemma or nucleated sheath of Schwann, according to Kölliker, is derived from microblasts; other authorities believe the sheath cells to be derived from the ganglion crest. The actual origin of the myelin sheath is not clear, but it is in all probability a product of the functional activity of the neuraxon.

The study of the development of the nervous system, and observations made by the methods of Golgi and Cajal, have demonstrated that in vertebrates the essential nervous elements consist of complex cells, which are structurally independent, now almost universally spoken of as "neurones."

At one period of their development all these neurones are structurally the same, consisting of cells composed of spongioplasm and hyaloplasm, and containing nucleus and nucleolus. Processes grow out from the cells, consisting of delicate fibrillæ. These processes are essential parts of the cell, have the same biochemical nature, and are continuous with the cell framework. One of these processes gives off collaterals and becomes differentiated into the axon

fibre. The other processes, termed "dendrons," branch like the limbs of a tree, and terminate in a dense network of fibrils, studded with tiny gemmules (Fig. 1). Within the cell, lying in a spongy network, is the hyaloplasm. The staining method of Nissl shows that the spongioplasm and hyaloplasm differ in chemical constitution; the former is achromatic, and the latter readily takes up the twin dye (Plate I., Figs. 1, 2, 3, 4), and is termed "chromophilous."

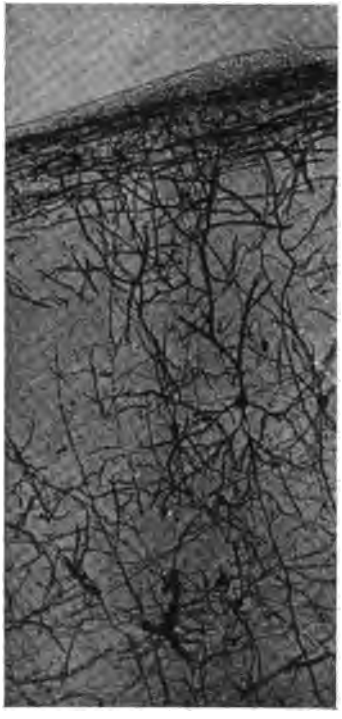


FIG. 1.—SECTION OF THE CRUCIAL SULCUS OF THE BRAIN OF A DOG STAINED BY GOLGI'S METHOD, SHOWING A LARGE PYRAMIDAL CELL GIVING OFF A LARGE BRANCHING APICAL DENDRON, AND DENDRITES, ENDING IN THE TANGENTIAL SYSTEM OF FIBRES.

Little buds, or gemmules, can be seen on the processes. (Magnification 80.)

The blocks of chromophilous substance seen typically in the large motor cells of the brain and spinal cord are termed "Nissl bodies." These consist of extremely small particles suspended in a fluid, and are said by some to represent simply stores of energy and food; but Marinesco and others hold that, by their rapid chemical changes during the passage of a nervous impulse, they serve to augment this impulse. In support of this view, it is interesting to note that these bodies are infinitely more numerous in the large cells directly concerned with movement, and may be

almost entirely absent in experimental fatigue. It will be observed that Nissl bodies can also be demonstrated in the dendrons, whilst they are entirely absent from the axon. In the majority of cells they are also absent in the immediate neighbourhood of the nucleus and in the extreme periphery of the cells. Marinesco suggests that their absence in these parts of the cell is due to the fact that a dense feltwork of neuro-fibrils exists in these places. These are continuous with the fibrils of the dendrons, and again meet to form the dense neuro-fibrillary system of which the axon is composed.

In all probability, the Nissl bodies do not exist as such in the living cell (since Ehrlich's intravitam methylene-blue method does not demonstrate Nissl bodies); but precipitation occurs on the death of the nerve cell, as in the case of myosin from dead muscle plasma. However, the results obtained by Nissl's method are of great value in the study of pathological conditions of the nervous system. Whether the granules are preformed or a result of cell death is not a matter of vital importance to the pathologist, since he knows that the large healthy nerve cell always presents Nissl bodies, while the diseased nerve cell lacks them altogether, or presents various alterations in their number, size, and distribution. Thus, the cell loses its characteristic Nissl pattern, and is said to exhibit a chromatolysis (see Plate I., Figs. 5, 6, 7, 8, 9, and Plate II.).

Marinesco and Cajal have shown that many changes take place in the neuro-fibrils of the nerve cell as the result of disease. These changes give rise to a granularity of their substance, and to a change in their staining reactions, while in extreme cases fragmentation takes place.

The nuclei of nerve cells are extremely varied in shape, accommodating themselves to the forms of the cells in which they are placed. They consist of a definite nuclear membrane, which contains an achromatic fibrillar network. In the interstices of this network granules can be demonstrated, some of which stain with acid, and some with basic dyes. Towards the centre of the nucleus one or more nucleoli can be observed, the central parts of which stain strongly with the acid dyes, while the peripheral parts are stained more or less strongly with basic dyes.

The neuro-fibrils correspond with the achromatic substance, unstainable by basic dyes; the hyaloplasm lies in the interstices and is basophil. When the cell dies, chemical changes occur, one being the precipitation of a nucleo-proteid substance contained in the cytoplasm, which is basophil in reaction; this fills up the interstices and compartments between the fibrils. Thus the Nissl pattern is formed. It is a debatable point, and it is even improbable, that a division into neuro-fibrils and basophil hyaloplasm exists in the living cell. It is much more probable that the cytoplasm is a single viscid plasm of remarkable chemical complexity, and the passage of stimulus from one neurone to another determines lines of least

resistance in the cytoplasm of which the conductile substance consists, and a corresponding linear arrangement of molecules. The cytoplasm is surrounded by a periplasm, consisting of lipoids and cholesterol, which form an osmotic membrane permeable to O, $CO_2$, and Ca, K, Na ions.

Just as changes are observed in the Nissl bodies in conditions of fatigue and toxic poisoning, so also the nucleus shows marked changes according to the degree of fatigue or poisoning. In mild cases the nucleus reacts to stains very feebly, and a certain amount of vacuolation occurs. The nucleus is situated in the centre of gravity of the cell. As an indication of changes in the cytoplasm, the result of hydrolysis, the nucleus becomes swollen, clear, and excentric in position. It may lose its regular contour, swell up, and become vacuolated, and the intranuclear network disintegrated (*vide* Plate I., Fig. 7).

The conception of the morphological independence of the neurone has been questioned by Apathy, Bethe, and others. It is admitted that the nervous system consists of nerve fibres and nerve cells, supported by neuroglia. The main point of discussion has been the origin of the nerve fibres. Waller first showed experimentally that a nerve separated from its ganglion underwent degeneration, and it is admitted that there must be some intimate relation between the ganglion cells and nerves; but it has been disputed whether regeneration takes place by a new outgrowth from the cell of origin or whether it is effected by the cells of the sheath of Schwann. Likewise the genesis of the nerve fibres has been attributed by some to an outgrowth from the cell; by others it is considered to be a product of the sheath cells. Apathy, Bethe, Schultze, and others, hold that the nerve fibre is the product of a chain of cells which extend from the nerve cells to the peripheral termination, and they assert that these sheath cells secrete the fibrillæ within their protoplasm. His, by embryological experiments, demonstrated that the axis cylinder and the other processes of the nerve cell were the outgrowths of the cell protoplasm. Golgi, Ramon y Cajal, Kölliker, Retzius, Lenhossék, Van Gehuchten, and many others, by the chrome silver method and its modifications, apparently demonstrated the fact that the whole nervous system consisted essentially of independent anatomical units, and that the axon was an outgrowth of the nerve cell. Ramon y Cajal followed the development of the neurone from the neuroblast in all its stages, and confirmed the researches of His. Held also demonstrated that the nerve fibre was an outgrowth of the nerve cell. Ross Harrison, by his experiments on the embryo of *Rana esculenta*, has shown that the nerve fibres grow independently of the sheath cells, and he has been able to show that the spinal motor neurones can be watched in their development, and the rate of growth of the axis cylinder measured. (He has observed a growth of 20$\mu$ in

twenty-five minutes.) Moreover. he showed that there is at the extremity of the axon of the living neurone a similar appearance to Cajal's cone of increase, and it is possible that it possesses an amœboid function. These observations of Ross Harrison show, beyond question, that the nerve fibre begins as an outflow of protoplasm from cells situated within the central nervous system. This protoplasm is actively amœboid, retaining its pseudopodia at its distal end; the protoplasm is drawn out into a thread, which becomes the axis cylinder of a nerve fibre. Although Harrison has disproved the theory that the sheath cells form the essential portion of the nerve—namely, the axis cylinder—yet he fully admits, as all those who uphold the neurone doctrine do, that the cells of the sheath of Schwann play an important rôle in the nutrition and production of the nerve fibre.

These experiments of Ross Harrison place the outgrowth theory of His upon the safest of all foundations—namely, that of direct observation. It is, moreover, interesting and important to note briefly that Marinesco, Goldstein, Minea, and Nageotte, have observed in transplanted spinal and sympathetic ganglia of warm-blooded and cold-blooded animals an outgrowth of fibrils from the ganglion cells. As Verworn truly says, the embryological basis of the neurone doctrine has been established beyond dispute. The formation of connections of one neurone with another by fibrils, the passage of fibrils from one nerve cell through another nerve cell, are matters of detail which in no way shake the fundamental principle of the neurone concept—namely, that the cell and its processes form a nerve unit which has a genetic independence.

According to Kölliker, all the nerve fibres arise from nerve cells of the central nervous system and the ganglia. The peripheral nerve fibres are surrounded by special cells, constituting in the adult the sheath of Schwann. The latter appear when the axis cylinder is developed, and constitute for it a superficial envelope. These sheath cells all arise from the mesoderm, and multiply by karyokinesis. According to Froriep, however, the cells of the sheath of Schwann of the peripheral nerves are probably like the neuroglia cells of ectodermal origin. Certainly Harrison's experiments seem to support Froriep's views.

The cerebrospinal neurones may be divided into afferent, efferent, and association systems. The last, however, are by far the most numerous; the great bulk of the brain substance consists of association neurones.

**Theories of Interneuronic Relationship.**—All the above systems are in physiological relationship. The nervous impulses are propagated towards the body of the cell by the dendrons, and away from it by the axon. It was first suggested by Demoor as a conceivable hypothesis, that, in a system or series of nervous units with multitudes of points of contact, retraction of the dendritic

processes of one from contact with the terminal arborizations of another would lead to considerable differences in the rate of passage and intensity of nervous impulse.

Many apparently inexplicable phenomena relating to normal and pathological functional conditions of repose or activity could be satisfactorily explained by such a theory of approximation and retraction of the interneuronic connections. Such a theory, unfortunately, has, up to the present time, very slender support from experimental observations. Many movements of the nerve cells have been observed under the microscope in the case of small aquatic animals. So it was conceived that the dendrites might elongate, and so bring into contact the minute gemmules which stud these terminal arborizations.

Against such a view, Marinesco points out that these gemmules are never invaded by neuro-fibrils of the dendrites, which presumably conduct the nervous impulse.

This led to the idea that sleep, unconsciousness from anæsthetics, catalepsy, imperception, and other conditions, such as trance, hypnotic state, hysterical palsies, anæsthesia, and numerous symptoms of nervous disease—*e.g.*, catalepsy and katatonia—might be due to retraction of the terminal twigs of the sensory neurones in the cerebral cortex, so that contact is broken and the passages of nervous impulses is more or less interfered with. Observations by Hill and Mott of changes in the cortical cells after ligation of all four arteries in animals do not support this doctrine. Moreover, attempts to solve these questions by fixing pieces of brain tissue of animals killed while under the influence of anæsthetics and narcotics, and comparing the dendrites with those of animals killed suddenly, have given such diverse results in the hands of different observers that no satisfactory conclusions can be drawn.

Lugaro, as the result of his experiments on this subject, has suggested the diametrically opposite view—viz., that cerebral and synaptic activity generally are due to a withdrawal of most of the dendrites from contact, thus leading to an intensification of the current passing through a few from lessened diffusion of energy. According to this view, there is, during anæsthesia and repose, a general approximation of the gemmules, due to loss of their contractility, which is brought about by the toxic effect of the anæsthetic or of fatigue products. Thus, all the gemmules being in contact, afferent impulses are so diffused that they are not of sufficient intensity to rise into consciousness.

Sherrington and others would suggest that the above-mentioned phenomena are due to changes taking place in the conductile power of the interneuronic substance, or synaptic membrane, as it has been named; *e.g.*, conditions of mania might, on the one hand, be explained by some toxic alteration of the synaptic membrane,

leading to general diminution of its resistance, and thus accounting for the general hyperæsthesia, the extraordinary rapidity of the association of ideas, and the psycho-motor restlessness; while, on the other hand, symptoms and signs of a depressive psychosis, with loss of volitional initiative and emotional indifference, could be explained by some toxin giving rise to a biochemical change in the synaptic substance, causing a general increase of resistance to the passage of stimulus. These are mere hypotheses, and there is no reason why the poisons should not affect the whole neurone.

**Chemistry of the Nerve Cell.**—This subject can only be briefly touched on here, and only in so far as the chemical constitution of the nerve cell differs from that of other cells of the body.

The most striking thing to be noticed is the large percentage of lipoid substances in the nerve matter, the most important of these being undoubtedly lecithin, a complex fatty body containing phosphorus and nitrogen. Cholesterol, another of the lipoid substances, occurring in large amounts, has most of the physical properties of a fat, but is in reality an alcohol.

These lipoid substances are of extreme importance to the cell, forming as they do the most important constituents of the semi-permeable membrane which forms the peripheral portion of the cell.

Many substances which dissolve in these lipoids readily permeate the cell substance, among others chloroform and ether, and this probably accounts for their rapid action in lowering cerebral activity.

Nerve cells are also rich in nucleo-proteids, some of which—*i.e.*, the Nissl granules and parts of the nucleus—contain highly unsaturated nucleic acid radicles; hence their great affinity for basic dyes.

Apart from the larger percentage of these substances, the chemical constitution of the nerve cell calls for no further comment, since the chemistry and physics of cells generally are fully discussed elsewhere.

**The Functions of the Neurone.**—Every neurone is a cell which is both excitable and conductible, and any stimulus applied to the receptive end is propagated through the whole neurone. A nervous impulse always circulates in one direction, and is never reversed. This phenomenon James has termed "the law of forward direction." An impulse in propagation along a chain of neurones is subject to modification, either in the ganglion cell, or it may be at the junction of the terminal process of one neurone with the processes of another (synapse). Whereas the nervous centre is easily fatigued by excessive functional activity, the nerve fibre is not affected under normal physiological conditions, consequently there must be some integrating substance or structure included in the reflex arc; this may be in the ganglion cell or in the synapse of Sherrington.

**Fatigue of the Ganglion Cells.**—Evidence of fatigue of the ganglion cells is afforded by a diminution of the basophil staining substance and nuclear changes. The nerve fibres show no visible alteration. The inference is that this substance contained in the ganglion cells and protoplasmic processes is used up by excessive functional activity. It need not be that the active chemical processes connected with nervous action occur in the cell; possibly the biochemical changes incidental to nervous activity take place at the terminal arborization of the nerve cell within the grey matter. Verworn has studied the phenomena of fatigue in the frog by the production of an artificial circulation of oxygen-free salt solution in the animal, and subsequent injection of strychnine. A maximum amount of work was then obtained on the slightest peripheral stimulation. The circulating fluid being oxygen-free, the strychnine allowed a store of oxygen-containing substance to be drawn upon. On cessation of the artificial circulation, with stagnation of the oxygen-free fluid in the capillaries, the tetanic spasms became gradually weaker, and finally no response was obtained. With restoration of the artificial circulation, the tetanic spasms could be again induced. In time, however, they became weaker, and occurred at longer intervals, and then ceased altogether. Presumably, then, the spinal motor neurones possessed a store of latent energy, which, under the influence of strychnine and a stimulus, could be converted into kinetic energy, independently of oxygen in the circulating blood. In order, however, to maintain a continuity of action oxygen is necessary, and when all reflex response is lost, the circulation of an oxygenated medium is sufficient to restore the excitability. Von Baeyer has been able in certain cases to obtain reactions in a frog for ten to twelve hours with a sufficient supply of oxygenated fluid, but without any nutritive material in the fluid.

It may be concluded, therefore, that two processes occur during excessive activity of the ganglion cells: (1) *Fatigue paralysis*, due to the accumulation of the products of destructive metabolism. (2) *Exhaustion paralysis*, owing to failure of repair of waste. This exhaustion may result from failure of oxygen storage, or, in exceptional experimental conditions, from failure of organic material.

Dr. Gordon Holmes has shown that if a frog be subjected to excessive work for a long time under the artificial condition of a circulation of oxygenated salt solution, the whole of the store of carbon-containing energy substance is oxidized out of the ganglion cells, and the spinal motor cells no longer contain Nissl granules. From this it may be inferred that this substance, which forms the Nissl granules, is used up by work.

Von Baeyer and Winterstein have shown that the ganglion cells of the frog can take up larger quantities of oxygen at lower temperatures because, with a rise of temperature, larger quantities of oxygen

are used up; therefore the addition of oxygen from without cannot keep pace at a higher temperature than normal with that which is used up within the neurones. At a temperature of 33° to 35° C. paralysis occurs in the frog owing to failure of oxygen—that is, a condition of asphyxia-exhaustion occurs which can only be remedied by a renewal of oxygen at a lower temperature. By analogy with other cells, it is to be inferred that the oxygen is diffused throughout the whole nerve cell in a state of chemical combination. The loss of function of the neurone may, therefore, arise from disturbances affecting different factors entering into its metabolism. The researches of Winterstein on the action of narcotics on the ganglion cells led him to the conclusion that narcotics paralyze the oxygen intake of ganglion cells, for when these cells have been exhausted of oxygen and then narcotized, they are unable to take it up even when it is supplied in abundance. These experiments tend to prove that narcotics hinder the transference of the molecules of oxygen from the oxygen store to the place where oxidation processes occur. The block to the use of the stored oxygen causes a functional paralysis of the neurone by a process of asphyxia. Excitation of the neurone and later exhaustion occur when the temperature of the body rises above normal. If oxygen is used up faster than it can be replaced and stored, exhaustion is the result, and the functional activity of the neurone ceases. It is not, however, destroyed unless the temperature rises so high as to produce a heat coagulation of the neuroglobulin. This change occurs in hyperpyrexia.

**Processes occurring in the Nerve Fibre.**—The processes occurring in nerve fibres during the transmission of an impulse have been recently the subject of numerous experiments. Von Baeyer has shown that a tetanized nerve in an atmosphere of pure nitrogen loses its irritability and conductibility. He has also found that a complete return to the normal may be brought about by admission of oxygen. The sheath may possess the power of storing oxygen or of replacing it as fast as it is used up; the experiment, however, proves that oxygen is stored and used up and that metabolic processes take place in this part of the neurone similar to those in the nerve cell, of which it is a process. It is probably incorrect to say that nerve is absolutely immune to fatigue, since Thörner has shown that a nerve in air can be brought into a stage of commencing fatigue by continuous tetanic excitation, and if a nerve be placed in nitrogen during this stage of commencing fatigue, it passes more rapidly into paralytic fatigue than a nerve not previously tetanized. These experiments of Verworn and his pupils on the neurone of the frog under various conditions of alteration of the circumambient medium are in agreement with those performed on warm-blooded animals, for it has been shown that when healthy neuro-muscular tissue is rendered anæmic, a stage of hyperexcitability of function

precedes that of paralysis, and further, that the onset of these two stages may be delayed by cooling the tissues.

**Reflex Action.**—A reflex action is produced by a stimulus which may be defined as a change in the environment which acts on the organism as an exciting agent. In the conception of a reflex action three structures are implied: (1) A receptor or initiating organ; (2) a conductor; (3) an effector. In the simple reflex each of these three structures plays its part, and Sherrington has shown that there has been evolved a perfect pre-organized automatic spinal reflex mechanism for each of which some particular biological stimulus is appropriate, in order to adapt the organism to its environment for the preservation of the individual and the species. The receptor plays a very important part, for it provides an increase of responsiveness to changes of environment, and at the same time limits its excitability to particular stimuli, and thus tends to avoid confusion of reflex responses and inco-ordination. Conduction in reflex arcs and nerve trunks shows the following differences: (1) The central rate of conduction is fifteen times slower than the rate in the nerve fibre. (2) The central resistance, while considerable for a single nervous impulse, is easily forced by a succession of impulses. (3) Instead of reversibility of direction of currents, as in nerve trunks, there is irreversibility. Gotch and Horsley have shown that there is a complete block to transmission from the afferent into the efferent neurones. (4) The cell is susceptible to fatigue; the nerves are comparatively insusceptible. (5) The central efferent discharge has a special periodic character. (6) The central efferent discharge may continue after the afferent nerve impulses have apparently ceased. (7) Refractory period (*Bahnung*), inhibition, and shock, exist in degrees unknown for nerve trunks. (8) There is a much greater dependence on blood-supply and oxygen than is the case with the nerve trunks. (9) There is a much greater susceptibility to various poisons, drugs, and anæsthetics, than is the case with the nerve trunks.

To explain the facts above related, on physical or chemical grounds, Sherrington concludes that there is a surface separation between neurone and neurone. He inclines to the physical explanation; thus the intercalation of a transverse surface of separation into the conductor must modify the conduction, and it would do so with the same results which are known to differentiate reflex arc conduction from nerve trunk conduction. Further, the passage of a stimulus through the fibrils of the cell, where the store of latent energy substance is deposited, may convert the latent energy into kinetic, and this may excite the delicate fibrillar tenticles to amœboid movements, which, after a shorter or longer delay, according to the effect of the biochemical stimulus, lead to the formation of innumerable ultra-microscopic protoplasmic bridges connecting the terminal fibrillæ of one neurone with those of another. Scott has

suggested for the biochemical explanation that the chromophilous substance of the ganglion cell is a store of organic material representing latent energy, and that in the presence of oxygen and a stimulus it is continually transformed into a substance capable of liberating active energy at the terminal points of the next neurone, and, discharging, excites the fibrillar terminals of the next neurone as soon as sufficient energy has developed. This conception would also account for delay and summation of stimulus. The term "synapse" has been applied to this alterable conductor, upon which so much of the functions of the central nervous system depends, and the study of which may possibly explain the mysterious problems of the neuroses, psychoses, and so-called functional diseases of the nervous system.

It will be convenient here to consider an hypothesis put forward by M'Dougall with regard to the important part played by the synapse, and known as "the drainage theory." The hypothesis

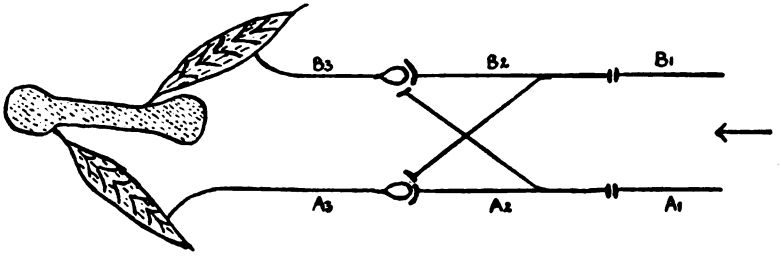



FIG. 2.—DIAGRAM TO ILLUSTRATE M'DOUGALL'S DRAINAGE THEORY.

was formulated to explain attention. In attention there is concentration of nervous discharge along particular and limited chains of neurones or functionally correlated systems, and withdrawal from the remainder. This presupposes a labile substance productive of nervous energy, which passes along certain lines of discharge, and M'Dougall postulates a substance—"neurogen"—which exists at the synapse and liberates energy. Now, if we represent diagrammatically two antagonistic neuro-muscular mechanisms—for example, flexor and extensor groups—by A1, A2, A3, and B1, B2, B3, the normal tonus at rest is equable between the two groups of muscles, because the stimulus is equable; but if a stimulus which requires a flexor response excites the skin, there will be a rise of potential in A1, A2, A3, and resistance will be diminished at the synapse. This will lead to a drainage of energy across from B1, B2. Then there will be an augmentation of outflow of energy to the flexor muscles with contraction, and a fall of energy in B1, B2, B3, with relaxation. By this means the maximum effect can be produced with the least expenditure of energy (Fig. 2).

Clinically the reflexes may be divided into two great groups:

1. Superficial cutaneous. These are plantar, cremasteric, and abdominal.

2. Deep or tendon reflexes.

On excitation of the skin the stimulus flows along the reflex arc to the motor neurones of the corresponding spinal segment, causing the muscle innervated by those neurones to contract. When a muscle, for example the quadriceps, is put on the stretch and sharply tapped, the muscle contracts, provided the reflex arc is intact. Bastian, however, has shown that in transverse lesions of the cord, caused by fracture high up in the cervical region, the knee-jerk is no longer obtained. He explains the absence of the knee-jerk by the removal of cerebellar influence, and it has been shown that his inference was correct, for it has been demonstrated that the phenomenon is due to the loss of the tonic influence, normally conveyed by the rubrospinal and vestibulo-spinal tracts, which are in intimate relation with the cerebellum by their connections with the dentate nucleus. Sherrington has shown experimentally that the bulbospinal axis contains a number of complex pre-organized neuronic mechanisms of an instinctive reflex nature. Thus the varied movements of the hind-legs of the dog are affected by a complex sensory motor mechanism capable of many different purposive reflex actions necessary for the preservation of the individual and the species—for example, to scratch, to walk, to run, to gallop, to squat in defæcation, etc.

However, the same muscles enter into the effector and are innervated directly by the same spinal motor neurones, which accordingly form a final common path for a number of such reflexes; but these activities would be liable to confusion were it not for the special selective possibilities of receptors, and the integrative co-ordinate adaptation necessary to fulfil a purposive action in response to a particular stimulus. Thus the character of the reflex evoked depends on the location of the stimulus, its quality, and intensity, and, to a limited extent, on its duration. Sherrington's experiments show that the character of a reflex may, as in the medusa and the beating heart, depend upon conditions of refractory phase. But they show more; they locate, in the grey matter, the seat of the refractory phase and the path by which the terminals of the afferent neurones of the reflex arc are associated with distant effector neurones which form the final common path for other reflexes.

Sherrington has also shown by his experiments on innervation of the ocular muscles that cortical stimulation produces both excitatory and inhibitory impulses. In conjunction with Hering, from experiments on antagonistic muscles of the limbs, he has shown that the result of excitation of the cortex was the discharge of both inhibitory and excitatory impulses of the lower spinal centres

by the pyramidal systems of fibres. He has also shown that the results obtained on stimulation of the fibres in the internal capsule were as striking as those obtained from the cortex itself. It is therefore probable that the inhibitory effect produced by cortical stimulation is not in these cases due chiefly, or even at all, to interaction of cortical neurones on one another. The fact that it is much easier to obtain flexor movements from cortical stimulation than extensor movements does not mean that the cortex is in touch with the flexors alone, and not with the extensors, but that the usual effect of the cortex on these latter is inhibition. It does not mean that the extensors and the jaw-closers are unrepresented cortically, but that their normal representation in the cortex under the ordinary circumstances of experiment has the form of inhibition, not of excitation, and this, unless specially sought, escapes observation.

**Conditional Reflexes.**—Pawlow has shown the important influence of psychical action upon organic functions and secretions. He found that the flow of the digestive juices was profoundly influenced by psychical impressions and by associative memory. By placing a cannula in the submaxillary gland of a dog, he found that the animal always secreted a larger quantity of saliva when acid fluid was put into its mouth. This he termed an "unconditioned reflex"; but if the fluid was coloured, and shown to the dog each time before it was put in the mouth, in a short time a conditional reflex was obtained, for it would then suffice merely for the bottle of coloured fluid to be shown to the dog to cause an increased flow of saliva to take place; but if once the conditioned reflex had been effected, it could not again be immediately obtained unless the unconditioned reflex had been previously effected. This may be interpreted as the establishment of an associative biorhythmical activity between the neurones of the sensory peripheral receptor and central receptor and the neural structures presiding over the lower unconditioned reflex. But when once the conditioned reflex has been fired off, this association is broken, unless an interval of time be left, or it be re-established at once by establishment of the unconditioned reflex. These experiments in many ways correspond to what is observed in many habits of daily life; thus, washing the hands causes a desire to micturate.

**The Affective Tone.**—"The organ of the mind (highest centre) represents all parts of the body; in strictly equivalent words, the highest centres are centres of universal co-ordination. It is thus that they are the organs of will, reason, memory, and emotion, the four elements of mind, or equivalents of consciousness" (Hughlings Jackson).

The study of nervous and mental diseases shows most clearly the important part which the affective tone plays in all forms of

disease, whether bodily or mental, for the affective life is the source and support of all stable actions of the mind. The affective life depends upon the organic sensibility, which, by ministering to the needs of the appetites and desires, becomes the active, although unconscious, source of the great majority of our habitual actions. The affective tone of the individual depends upon the functions of the vasomotor and vagal nerves; it is continually oscillating about a mean point of equilibrium, a mental state that is neither pleasurable nor painful. Although neither pain nor pleasure can be said to constitute an emotion, yet one or other, and sometimes both, form an essential part of every emotion. The preservation of the individual depends not only on the maintenance of the nutritional equilibrium by the gratification of the appetites, but the body is protected from physical and chemical injury by pain and the unpleasant emotion of disgust. Besides physical pain, many painful states may be related to the organic needs of hunger, thirst, the desire for sleep, for exercise, and, of especial importance, the desire to satisfy the sexual instincts; but, besides these physiological cravings, which play the dominant part in the conduct and habits of all human beings, there may be certain cravings induced by habit; for example, for alcohol, morphia, cocaine, etc., the discontinuance of which may cause physical and mental pain. In short, the sentient being, whether man or animal, reveals a combination, of appetites, of desires, of physical and psychical tendencies, and all those conditions, whether from internal or external causes, which suppress or interfere with them, give rise to painful states, physical suffering, and mental pain.

**Physical Pain.**—Painful sensation depends not only upon the intensity of the irritant applied, but also upon the irritability of the chains of neurones, which form the sentient system of receptor, transmitter, and perceptor. This is a matter of common experience, especially in disease. Pain is felt in the cerebrum; and without the cerebral centres there would be no pain, only irritability and reflex discharge, such as occurs in a decerebrate animal.

**Pain and its Conduction.**—Schiff taught that the grey matter is æsthesodic, and the white matter kinesodic. Syringomyelia, in which the grey matter is destroyed and the white matter uninjured, is characterized by a condition of sensory dissociation. The patient feels tactile sensations, but no longer feels pain, heat, and cold. There are many facts which show that Lissauer's tract contains the fibres which conduct painful sensation. The tract is degenerated in tabes dorsalis, but it is not degenerated in Friedreich's ataxy. Lightning pains and patchy analgesia, generally met with in the former, do not occur in the latter disease. It is probable that the reason that cocaine, stovaine, etc., when injected into the cerebrospinal fluid by lumbar puncture, produce loss of sensibility to pain without loss of movement is due to the fact that the synapse

of these fine fibres is close to the periphery of the cord ; consequently the drug readily permeates, and produces an effect thereon, interfering with conduction, whereas the synapse of the motor neurones is much more deeply seated. It also shows that the nerve fibres of these roots are probably not affected by the presence of the drug in the fluid.

Sherrington has shown that the impulse of painful impressions comes from one half of the body, leaves the grey matter, and passes up the lateral column of both sides, rather more on the opposite. The painful stimulus is transmitted to the brain, but there is no certain evidence that pain is represented in any part of the cortex. Painful sensations, together with all afferent sensory stimuli, meet in the optic thalamus, the principal function of which is that of a sensory relay station to the cortex. This mass of grey matter, including the external and internal geniculate bodies and pulvinar, sends afferent radiations to all parts of the cerebral cortex, but particularly to the projection centres about the primary fissures. It contains two forms of cells ; large cells, like those of the anterior horn of the spinal cord and the motor area of the cortex, and smaller cells. These large cells are, in all probability, motor in function, and control the subconscious, involuntary, instinctive, automatic, mimic reflexes of gesture, physiognomical expression, and of primitive vocalization. The evidence in favour of this is that experimental lesions in animals and spontaneous lesions in man invariably produce some degree of anæsthesia on the side opposite the lesion. Irritative lesions of the thalamus are frequently associated with severe pain in the opposite half of the body. Sir Charles Bell first pointed out that in old cases of cortical hemiplegia the face on the affected side can only be imperfectly moved by the will ; yet if the patient, under the influence of the emotions, laughs or cries, this side of the face is more strongly contracted than the non-paretic side. In lesions of the thalamus, on the other hand, the opposite is frequently observed. The patient, on the one hand, can voluntarily move the paretic side of the face well in all directions, as in showing the teeth, voluntary laughing, etc. ; on the other hand, in emotional expressional movements, this side of the face is immovable. According to Von Monakow, this condition is not met with in other cerebral lesions ; therefore, although it does not occur in every lesion of the optic thalamus, the fact that it does not occur in any other cerebral lesion indicates that some part of the thalamus is associated with these reflex mimetic movements. Von Monakow, moreover, cites cases which seem to show that it is possible that secretory, vasomotor, and other tracts of fibres in connection with the sympathetic nervous system have an abundant representation in the optic thalamus.

If painful stimuli be applied to the skin of a decerebrate animal, a number of reflexes are obtained, which Sherrington calls "pseudo-affective," because the neural mechanism for the perception of pain

is cut off from its connection with the receptor, but it is still in connection with a purposive instinctive reflex motor mechanism of offence and defence. Such a decerebrate animal, when the sciatic nerve is stimulated, exhibits movements as in progression, turning of the head toward the part excited, opening the mouth, retraction of the lips, movements of the jaw as in snapping, vocalization, angry in tone (sometimes plaintive, sometimes snarling), and with these a passing increase of arterial blood-pressure. These movements are ineffective and of brief duration, possibly because they are deprived of the perpetual reinforcement which the brain gives. Sherrington concludes, from experiments conducted with Woodward, that each lateral column conveys impulses from both halves of the body, and somewhat preponderantly from the crossed half, and this is true for these arcs, whether they be traced from skin, muscle, or viscera.

Goltz, by a series of careful experiments, was able to remove the whole of the cerebral hemispheres and a large part of the basal ganglia from a dog in successive operations ; the animal, by patient and careful feeding, was kept alive many months, and observations showed that all the instinctive reflexes may be present in an animal from whom practically all the hemispheres had been removed. It responded to stimuli, but it had no memory. Pagano has published a number of experiments on adult and new-born dogs, and claims to have demonstrated that excitation of the caudate nucleus and of the optic thalamus provokes in adult dogs movements of expression distinctly attributable to determined emotional states, accompanied by visceral phenomena. From his experiments he concludes that in the basal ganglia are found at birth physiological pre-organized mechanisms of emotional reaction. The cerebral cortex, not being functional at birth, is therefore not indispensable for these emotions. He concludes also that the superior psychical centres, which are superimposed on the lower centres, are only a new source of stimulus for primordial expression, but, at the same time, the origin of secondary modifications of emotional expressions.

Sherrington has also shown that an animal whose brain has been cut off from its connection with the heart and viscera generally, still exhibits joy and sorrow, anger and fear, disgust and sexual instinct. In the normal and quiescent, non-emotional state, an equable reflex tonus by afferent stimuli is maintained in somatic respiratory and viscero-vascular muscle, but under the influence of emotion (rage) there is a surcharge of nerve potential flowing out through the somatic and respiratory systems of neurones ; consequently there may be a drainage away of the normal flow of potential by the viscero-vascular neurones, and a vascular dilatation will occur, or the vascular dilatation may be explained by antidromic discharge along the posterior roots, which may, as experiments by Bayliss prove, lead to vaso-dilatation. We are made conscious of

this change in our own bodily state by the afferent impressions to the brain from the skin, muscles, and viscera, but mainly the two former, and these impressions will arise in the whole column of sensory cells, somatic and visceral, from the top of the fifth nucleus to the end of the spinal cord. Before reaching the seat of consciousness, however, these impressions will all be projected into the thalamic grey matter, where a fresh relay of neurones occur. But the thalamic region is also a station for receiving impressions from the special senses—hearing, sight, touch, taste, and smell—where relay neurones occur by which the several special sense stimuli are conveyed to definite regions of the perceptive cerebral cortex. *The thalamus may thus be the great subconscious centre for the elaboration, integration, and co-ordination of sensory impressions derived from organic changes in the body, and those brought by the special senses from the material world around.* The thalamus is connected with the corpus striatum, and it is possible that both the basal ganglia may be primary centres of emotional discharge to the lower centres.

**Neuroglia.**—The neuroglia, or supporting tissue of the nervous system, remains for consideration. For demonstrating this structure Mott has found the Heidenhain iron method counter-stained with eosin to give the best results. When this process is employed, the structure of the separate neuroglial cells, and the mode of their proliferation and hyperplasia, is readily discernible in sections of the central nervous system. The nuclear membrane, the contained nucleoli, and chromidian granules, are stained deep blue, and the cytoplasm pink; the branching processes of the cells in a more advanced state of development are stained deep purple. All phases in the development of these neuroglial cells can be observed in chronic inflammatory conditions, also in degenerative processes of the central nervous system.

The neuroglial cells may, for reasons not known, undergo active proliferation in the central nervous system leading to the formation of a gliomatous tumour. Proliferation of the glial cells takes place, the nervous substance is infiltrated and pushed aside, the neural elements may even be destroyed. In syringomyelia, an increased amount of embryonic tissue in the form of neuroglia may persist around the central canal of the spinal cord; with this there is an increase of thin-walled vessels which are liable to rupture, and the effused blood may cause a destruction and hollowing out of the grey matter with corresponding loss of function.

Weigert, in 1890, formulated the following law: "When, from whatever cause, nervous tissue disappears, the neuroglia always reacts by a nuclear and fibrillar proliferation." In 1894 Nissl stated that when a nerve cell, directly attacked by a noxious agent, undergoes a regressive transformation, the surrounding neuroglial cells present a progressive transformation. Stroebe, Nissl, Lugaro, and

Marinesco, showed that neuroglial cells surround the nerve cells of the cortex in the normal state.

In secondary degenerations the place of the nerve fibres is taken by proliferated neuroglial tissue (sclerosis). In disseminated sclerosis tracts and islets of nerve fibres are gradually replaced by dense neuroglial tissue, especially fibrils; this, however, is secondary to destruction and absorption, first of the myelin sheath, and later of the axon. According to Nissl, the neuroglia plays an important part in the destruction of the nerve cells, the neuroglial cells becoming more apparent in pathological processes, and absorbing the products of degeneration of the nerve cells. Marinesco also considers that the neuroglial cells have a phagocytic function, and he terms it *neuronophagy*. Ossokine maintains that this neuronophagy is a secondary phenomenon, occurring only as a result of profound modifications of the nerve cells. Bevan Lewis long ago pointed out that the neuroglial cells of the central nervous system exercise a phagocytic action. Alzheimer recognizes that in certain circumstances the neuroglial cells may contain in their interior granulations and detritus of very different nature and origin; but he does not consider that it has been proved that the group of proliferated neuroglial cells, existing around and even in the interior of nerve cells can possess a phagocytic function. He contends, rather, that they serve to refill the place left free by the destruction of the nerve cell. The proliferation of the neuroglial cells seen in acute toxic conditions is explained by Mott as probably due to the failure of assimilative metabolic processes of the nerve cell as a result of the poison, the consequence being that there is more nutriment at the disposal of the neuroglial cells, whereby they are stimulated to proliferation.

### Degeneration and Regeneration.

There is no evidence to show that, if neurones are once completely destroyed, they can ever be replaced. However, it is extremely important to remember in this connection that a functional defect, due to a lesion in one area, may entirely clear up by compensation occurring in another area. This is especially to be noted in the cases of young patients. In the cerebrum and cerebellum of young patients even large lesions may be compensated for either by the adjacent cortex being educated to take up the functions of the destroyed area, or, as is perhaps more common, the opposite side of the brain may take up the functions of the lost elements.

Compensation takes place very readily in the cerebellar cortex; hence a lesion here must be progressive to give lasting symptoms of its presence. This is only to be expected when we realize the fact, pointed out by Horsley and Clarke, that the cerebellar cortex has no differentiation of function, but is only an afferent relay

station on the way to the paracerebellar nuclei, the most important of which are the roof nuclei of the middle lobe and the dentate nuclei of the lateral lobes.

In the conducting tracts of the internal capsule, brain-stem and spinal cord compensations cannot occur unless there be choice of paths. Again, even where such choice exists—viz., in the case of the pyramidal and pre-pyramidal systems (cerebro-thalamo-rubral system)—as age advances, from infancy upwards, each tract develops its own special function, and in the higher mammals the pyramidal tract becomes increasingly more important. So that, except in infancy, lesions of the pyramidal tract are never more than partially compensated for. However, a lesion of the pyramidal tract below the thalamus may be almost completely compensated for by the pre-pyramidal system in very early life. Yet such instances must be extremely rare, and for the most part destructive lesions of the efferent tracts are compensated for very inadequately.

Waller showed that, when a cell is cut off from its trophic and genetic centre (cell of origin), degeneration of the portion separated takes place. This process of degeneration is simultaneous throughout the whole peripheral portion of the nerve. Whereas there is now complete proof that regeneration of peripheral nerves takes place after section, the evidence of such regeneration of fibres within the central nervous system is scanty. Nevertheless, Marinesco and Minea have obtained evidence histologically of regeneration in the posterior and lateral columns, after division of the cord in the mid-dorsal region, where primary suture has been performed. They also report definite evidence of regeneration in two cases of fractured dislocation of the vertebral column in the dorsal region, with resulting transverse lesion. In both cases some months had elapsed between the time of accident and death.

When a peripheral nerve is cut across, or even an inch or more resected, regeneration will in time take place. The process of regeneration will be greatly hastened if the divided ends are sutured, or, where a piece of nerve has been resected, the regeneration time will be shortened by joining the cut ends with strands of catgut, decalcified bone, or other means of support, to conduct the downgrowths of the axons from the proximal to the peripheral end of the cut nerve. It can be definitely said, from the work of Vulpian, Howell and Huter, Ramon y Cajal, Perroncito and Marinesco, Langley, Anderson, Mott and Halliburton, and others, that, if the peripheral end of the nerve is prevented from anastomosing with the axons from neighbouring structures—*e.g.*, cut ends of skin nerves divided in the operation—regeneration of the peripheral axons never takes place.

The rapid return to sensibility that is sometimes observed after reunion of a nerve by immediate suture has led some authorities to believe in reunion by first intention. However, the extremely

careful work of Head and Sherren offers a complete explanation of these cases. They showed that the deep sensation of subjacent parts, such as would be elicited by the slightest pressure, is entirely independent of the cutaneous sensation, which should always be investigated by the lightest touch with cotton-wool or a camel-hair brush, so as to avoid actual pressure. The fibres subserving deep sensations of all kinds run with the motor nerves, and are hence not destroyed by division of all the nerves to the skin. Again, the overlapping of the skin distribution of superficial nerves must be remembered in this connection.

**Histology of Degeneration.**—Waller formulated the law that every part of a nerve which is separated from its cell of origin undergoes degeneration, *whilst the rest remains normal;* but this required modification, and Dr. Dickinson pointed out that the posterior roots atrophy, though still in connection with the ganglia, and anterior roots likewise, though still in connection with the anterior horn cells. A little later Von Gudden commenced his celebrated work upon atrophy of the cells of origin of a nucleus, by tearing out the nerve in young animals; and this method, with its further application by Forel and Von Monakow, threw a flood of light upon the anatomy and pathology of the nervous system. The researches of Nissl, Marinesco, and others, show that, when a nerve is divided, definite structural and biochemical changes occur in the cells of origin of the cut fibres.

The first change to be noticed in the nerve cells appears within twenty-four hours of the nerve section. The cell with its nucleus and nucleolus are swollen, and the form of the cell becomes more spherical. This increase in size of the cell may be explained by biochemical and biophysical changes within the cell, leading to alterations in osmotic conditions, and can readily be accounted for by the rapid breaking down of the cell colloids, which possess practically no osmotic value, into crystalloids, which, having a much higher osmotic value, determine a flow of fluid from the surrounding lymph spaces and cell canaliculi into the cell body, thus altering its shape and increasing its size. Twenty-four hours later there appear changes in the Nissl bodies, which become disintegrated and powdery, or, in other words, chromatolysis begins. This change first occurs in the granules in the neighbourhood of the nucleus, at the base of the cone of origin of the axon, which has been peripherally divided, and then later spreads to the remainder of the cell granules, and lastly to those in the dendrites.

About the fourth or fifth day the nucleus becomes excentric, and more or less irregular in form. As Marinesco and Cajal explain, this excentricity of the nucleus by the disintegration of the perinuclear fibrillary network, takes place *pari passu* with the changes of the Nissl granules, so that the alteration in the position of the nucleus is probably a passive one, and dependent upon the

amount of disintegration of the perinuclear fibrillary network of the cell. These changes become much more marked, and, indeed, total disintegration of the cells of origin takes place where nerves have been torn out as the result of accident or experiment.

This reaction of injury to the nerve cell, when its axis cylinder process is injured, is in direct confirmation of the correctness of the neurone doctrine, for if the sheath cells formed the axon, it is much less likely that the nerve cells would show changes which may even proceed to their atrophy and disappearance. It is a remarkable fact that when a nerve has been divided, only some of the motor spinal ganglion cells are so severely damaged that they are unable to recover. In polyneuritis, too, some cells show little or no change, while others eventually atrophy and disappear. Again, in transverse lesions of the spinal cord, Marinesco and Gordon Holmes have shown that the Betz cells of the cortex may be very unequally affected, an apparently undamaged Betz cell being found side by side with one seriously damaged, from which it must be concluded that the specific vital energy of some cells is greater than others.

**The Appearance of the Nissl Granules in Pathological Conditions, and their Significance.**—The appearance of the Nissl granules has long been one of the most valuable indications which the neurologist possesses for the study of the changes of the ganglion cells resulting from disease, and, provided that certain precautions are taken, valuable inferences can be drawn by comparing sections of normal nervous structures with those presumably diseased after fixing, cutting sections, and staining the same by the Nissl method. The granules were at one time believed to be an essential constituent of the living cell, but the researches of Hardy have shown that there is a great difficulty in deciding to what extent structure, demonstrable in the fresh or fixed state, is the product of chemical and physical changes, which constitute the death changes, or is due to the action of fixatives. Moreover, Held and others have shown that the *intra vitam* methylene-blue method does not reveal Nissl granules in the cell. The stainable chromatic or chromophilic substance, therefore, is probably not present in the living cell in the definite form in which we see it when the tissues are fixed and stained by the Nissl method. It must not, however, be assumed, therefore, that the method is unreliable as a means of studying the biochemical changes occurring in the protoplasm of the neurone, for, provided certain precautions are taken, it has proved most valuable in demonstrating functional and organic changes occurring in the nerve cells as a result of (1) injury of the axon; (2) exhaustion from excessive fatigue; (3) toxins circulating in the blood; and (4) hyperpyrexia. The large motor cells of the cord and brain are the best for studying the changes in the cell protoplasm, because in these structures the stainable substance appears in normal

# PLATE I

1. Large Betz cell from human cerebral cortex, showing the cone of origin of the axon at the base.

2. Medium-sized pyramidal association cell.

3. Anterior cornual cell.

4. Posterior root ganglion cell.

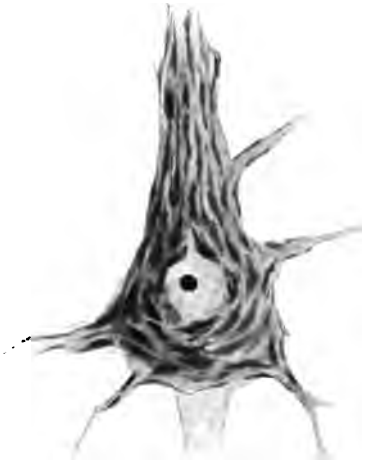
5. Shows a pericellular chromatolysis of an anterior horn cell. It will be observed that there are a few chromophilous elements around the nucleus still present; the cell is swollen, the nucleus is displaced, the cytoplasm exhibits a homogeneous appearance. (Preparation from a case of amaurotic idiocy.)

6. Shows a perinuclear chromatolysis. Endosmosis has taken place, the nucleus has become displaced and is excentric, and the chromophilous elements are only seen at the periphery of the swollen cell.

7. Shows degeneration, but with vacuolation of the cytoplasm.

8 and 9. Show a diffuse staining of the whole cytoplasm, such as may occur in hyperpyrexia, or in ischæmic necrosis.

# PLATE I



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tissue after fixation, as if it consisted of formed elements (Nissl granules) in the body of the cell and in the dendrons. Mott regards these elements as being caused by a death change of the cell plasm, whereby the nucleo-protein contained in it is thrown down as a fine precipitate, as myosin is precipitated from myosinogen. If this substance is abundant in the fluid plasm, it produces, when precipitated, these definite forms, because it fills up the spaces of the unstained intracellular fibrillar reticulum. Gordon Holmes has shown that the neuro-fibril may persist and the axons retain their myelin sheath when the Nissl substance has disappeared from the cell.

Two forms of chromatolysis may be met with: 1. Central or perinuclear, where the changes begin at the cone of origin of the axon and extend to the perinuclear region. This is met with in the anterior cornual cells in the various forms of peripheral neuritis, also in the Betz cells in alcoholic and lead polyneuritic psychosis. It is a characteristic lesion of the motor cell when the cylinder axon is divided. 2. Diffuse, in which the Nissl granules are absent, and the whole cell, with its dendritic processes, is diffusely stained by the basophil dye. This indicates a serious biochemical change, such as occurs in hyperpyrexia, or a change due to fatigue products and exhaustion, such as occurs in some cases of status epilepticus. In high fever, resulting from microbial toxæmia, there is a combination of central and diffuse chromatolysis.

Signs of regeneration in the cells begin to appear about the third week in young subjects, the earliest signs of improvement being the reintegration of Nissl granules and neuro-fibrils in the neighbourhood of the nucleus. Soon after this the nucleus regains its central position, and lastly, about the fifth to the seventh week, the cell finally loses its turgescence, and returns more or less to its former volume.

The following changes are observed in the peripheral nerve in specimens stained with osmic acid: Within twenty-four hours the myelin sheath begins to lose its straight outline, and to present an irregular appearance. The next day changes can be recognized in the axis cylinder process. It is swollen in some places, thin in others, and the myelin begins to break up. A little later the axis cylinder ruptures. On the third day the nuclei of the primitive sheath show signs of mitosis, the prelude of nuclear and cellular proliferation. On the fourth or fifth day there are evidences of proliferation of the nuclei and surrounding protoplasm, and these new-formed cells, breaking through the sheath of Schwann, cause a still further fragmentation of the myelin, which progresses until the tenth day. The appearance of the degenerated fibres on the eighth to the tenth day is characterized by a series of swellings, alternating with constriction. The swellings are due to accumulations in the

# PLATE II

1. Shows a perivascular chromatolysis of the posterior spinal ganglion cells in a case of chronic alcoholism. Some of the ganglion cells seem to be undergoing disintegration.

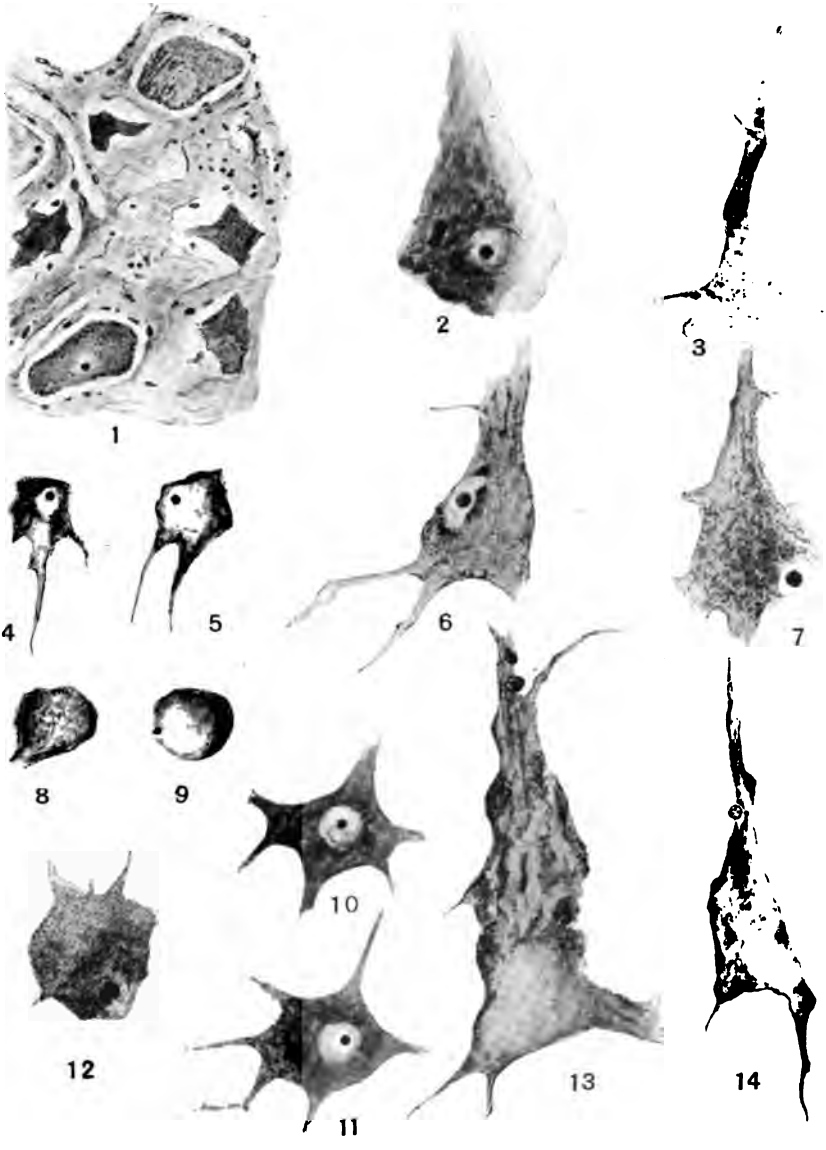
2. A large Betz cell from the cortex showing degeneration, the result of ischæmia produced by experimental ligation.

3, 4, 5, 6, 7, 8, 9, and 12. Show various appearances presented by cortical ganglion cells in animals in which both carotids and both vertebrals have been ligatured; those in which there is diffuse homogeneous staining are dead (3 and 12). The marked swelling of the nucleus shown in 8 and 9 is very characteristic of the effect of experimental anæmia.

10 and 11. Cells from the anterior horn of the spinal cord in a case of hyperpyrexia showing disappearance of the Nissl granules and a diffuse homogeneous staining of the body of the cell and processes due to a chemical change in the protoplasm.

13 and 14. Large Betz cell and large pyramidal cell from the cortex, showing marked chromatolysis due to experimental anæmia.

# PLATE II

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nerve tubules of degenerated myelin globules, proliferated nuclei, and protoplasm. On the fifteenth day the fibres in the greatest part of their course consist of tubes containing protoplasm, proliferated nuclei, and little or no myelin; but here and there, alternating with the constricted portions, may still be observed irregular swellings caused by distension of the sheath of Schwann, with drops of altered and liquefied myelin, nuclei, and often curled-up portions of the axis cylinder.

The degenerated myelin is removed by leucocytes—hence the origin of these cells containing fat-staining granules which can always be observed surrounding a degenerating fibre. The nerve eventually consists of fibrous tissue and shrunken tubes containing proliferated nuclei and protoplasm. This latter becomes fibrillated, and thus prepares the way for the new axis cylinder processes, which will grow down from the central end of the divided fibre.

The changes which occur in the proximal end of a divided nerve were only very incompletely understood before the introduction of the silver impregnation method of Cajal, whereby a new light has been thrown upon the process of regeneration. Perroncito has shown microscopically that active nutritive changes commence almost directly after the injury, and before the sheath cells divide. Marinesco has confirmed these observations. He has found that within twenty-four hours of section of the sciatic nerve there is evidence of increased nutritive activity shown by a swelling and hypertrophy of the large axis cylinders, and the constituent nerve fibrils, which make up the axons, become evident. A longitudinal fibrillar dissociation of the axon takes place, leading to the formation of a large number of embryonic fibrils, from which a number of young axis cylinders develop. These fibrils can be followed through the proximal cut end to the cicatrix. Some are seen to end in a button, olive, or club-shaped extremity, or helicoidal formation, forming a cone of growth which penetrates between the more or less longitudinally arranged sheath cells. At the termination of the cut ends there is a cellular exudation, with newly-formed capillaries. At the end of six to seven days organization of the exudate has united the two cut ends, and a passage is thereby afforded for the new fibres; but in proportion as the axon fibres penetrate to the cicatrix they diminish in number, and their branches are less numerous. The new fibres diverge, intercross, and form a network. A certain number of them, however, can be seen taking a straight course, and descending vertically in the peripheral stump. Cajal considers that the terminal bulbs correspond to the cone of growth of the developing axon in the embryo or pseudopodia in the advancing axon of the neurone observed by Harrison in his experiments. Cajal is probably correct in maintaining that the terminals of the new-formed young fibrils correspond to an amœboid phase of very

# PLATE III

FIG. 3, *A*.—Resection of 2 centimetres of sciatic nerve of a dog, showing attempts at regeneration fifteen days after the lesion. The neoformative reaction is shown in the form of new regenerating fibrils. Numbers of these are terminating in bulbs or spinals, some are penetrating into the tissues. (Magnification 120.)

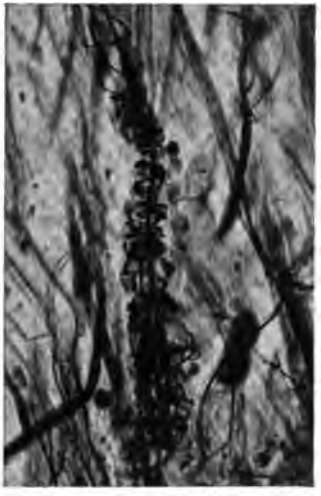
FIG. 3, *B*.—Same, under a higher power. (Magnification 400.)

FIG. 4, *A*.—Section under high power to show the neoformative reaction of repair after section of a sciatic nerve of a kitten, one month after operation. Active regeneration has occurred, as shown by the outgrowth of neurofibrils across the seat of the lesion. These fibrils in great numbers have penetrated the peripheral stump of the nerve, and active regeneration is taking place. (Magnification 300.)

FIG. 4, *B*.—The same, under low power. (Magnification 80.)

# PLATE III

A



B

FIG. 3.

A

B

FIG. 4.

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active growth, which assures the neurotization of the peripheral end of the divided nerve. After the stage of active ramification or dendro-amœboidism, numbers of terminal clubs of the young fibres are seen. These traverse paths rendered free to their passage between the sheath cells. Marinesco thinks that these terminal clubs only indicate a delay or retardation of chemotropism of the sheath cells. The shape of these terminal bulbs, which are so striking a feature of the regenerating nerve fibrils, is variable; in structure they consist of a network or twisted skein of fibrils, in the form of an olive or bulb, and an interfibrillar amorphous substance. It is difficult to decide whether these bulbous terminals represent cones of growth or a twisting up of a fibril on account of an obstacle to growth or nutrition of the nerve fibril. Three successive stages, therefore, can be observed microscopically at the junctions of the proximal and distal ends: (1) The sprouting of new fibres from the proximal end of the divided axon; (2) the penetration of the bridge of young vascular connective tissue, joining the cut ends by young nerve fibres; (3) the penetration and growth downwards of these young fibres between the proliferated sheath cells of the peripheral portion. Forssmann believes that the degenerated myelin exerts a chemotropic influence upon the developing fibrils of the cut central end of the nerve. Cajal and Marinesco, however, assert that the sheath cells secrete a chemotropic substance, which attracts and nourishes the young regenerating axon. All experiments, however, show that an outgrowth of the neurone takes place, and that, as the cell processes grow down into the new sheath, an interaction takes place between the new axis cylinder and its sheath leading to the formation of intervening myelin (Fig. 3, *A* and *B*, and Fig. 4, *A* and *B*).

Head suggests that the early appearance of what he has called "protopathic phenomena" is due to the presence of only the fine fibrils, while he has shown that the return of epicritic sensation is synchronous with the regeneration of the coarser fibres in the nerve. The superfluous new axis cylinders gradually atrophy and disappear.

At first the new-formed fibres are non-medullated, but later they acquire a medullated sheath, and nodes of Ranvier are formed at short intervals, as in the nerves of the growing embryo. In the scar, primitive sheaths are at first wanting, but they ultimately form from the surrounding connective tissue. It may take months or a year, or even more, before function is restored. The time required for regeneration and return of function varies with the length of nerve beyond the point of division, with the distance between the cut ends, and with the age of the patient. Sensation returns before movement when a mixed nerve has been divided.

Among other phenomena noticed by Head, and later by Trotter

and Davies, as the result of division of sensory nerves in their own bodies, two call for special mention here—viz., (1) the hyperæsthesia and hyperalgesia irregularly present in the neighbourhood of the anæsthetic area; and (2) the loss of localizing power and reference of pressure sensations to neighbouring skin areas. It must be remembered that each of these peripheral nerves is made up of fibres going to several spinal segments, in the case of nerves to the leg and arm, so that the cell changes and the by-products of their altered metabolism brought about by the division of one peripheral nerve will determine foci of irritation in several segments. If such a view be accepted, it is easy to understand the presence of hyperalgesia and hyperæsthesia of areas of skin subserved by fibres which pass through these irritated spinal segments.

Again, the reference of pressure over the area of altered sensation to neighbouring areas of normal skin, which Langley and Anderson have explained by the ingrowth of anastomotic branches from neighbouring nerves, may be simply a question of referred tactile sensation due to the passage of fibres from the neighbouring skin through the irritated segments, as is the case with referred pain in visceral disease.

**Chemistry of Degeneration.**—The great interest and importance of this subject centres round the products of disintegration of the cell lipoids, and the pathological appearance of a great increase of stainable fat in nervous tissue. The appearance of this stainable fat is a matter of extreme importance to the pathologist, since, were it not for this fact, the Marchi method would be useless as a means of recognizing degenerated fibres, depending as it does on the chemical affinity between osmic acid and free fat. Osmic acid, when used in pure solution, will stain normal nerve fibres. This is due to the fact that in the lecithins, besides the saturated stearic and palmitic fatty acid radicles, there is a considerable proportion of the unsaturated oleic acid radicle combined to form oleolecithin. It is this oleolecithin which is readily oxidized by the osmic acid to a black compound. But normal nerve fibres cannot be stained black when seen in section by Marchi's method, owing to the presence of the potassium bichromate, which, consisting as it does of small molecules electrolytically active—*i.e.*, ionizing readily—penetrates the semi-permeable membrane of the nerve fibre much more rapidly than the large molecules of the osmic acid, thus early fixing the unsaturated oleic acid radicles. On the other hand, in the case of degenerated nerve fibres the integrity of this semi-permeable membrane is broken down, and the osmic acid readily comes in contact with the increased stainable fat. In this reaction the osmic acid ($OsO_4$) readily gives up its oxygen, being reduced to $OsO_2$; while the fat is oxidized, forming a black compound which is easily recognized, since the osmic acid

cannot, as has been explained, so readily attack the combined fat of healthy nervous tissue, which therefore remains in contrast stained a pale brownish-green colour.

The origin of the fat has been widely discussed, and the desire to solve this question has led to a great deal of research. Observers seem to be agreed on the following points, viz. :

1. That there is no quantitative increase in the total amount of fat to be extracted from nervous tissue which has undergone degeneration, as compared with normal tissue.

2. That the diminution in the lecithins which takes place in conditions of degeneration, although great, does not entirely account for the large amount of stainable fat found.

It is suggested that the fat exists mainly in chemical composition with the proteins, and that fatty degeneration is due to autolytic changes disrupting the compound protein molecule, and so making manifest the combined fat, which is then readily stainable by selective stains.

There are other extremely important chemical substances which are set free as products of disintegration of lecithins. The nitrogenous derivative of lecithin, cholin, belongs to the trimethylamine series, of which neurin, muscarin, and betain, are other examples. Cholin was at one time thought to be identical with neurin, and the two are very closely related, cholin being unstable and readily converted into neurin by bacterial and other agencies by the process of dehydration. This is of great importance, since neurin is much more poisonous than cholin.

The breaking up of the complex molecule probably takes place thus :

$$\underset{\text{lecithin}}{C_{44}H_{90}NPO_9} + \underset{\text{water}}{3H_2O} = \underset{\text{oleic acid}}{2C_{18}H_{36}O_2} + \underset{\substack{\text{glycero-}\\\text{phosphoric}\\\text{acid}}}{C_3H_9PO_6} + \underset{\text{cholin}}{C_5H_{15}NO_2}$$

**Cholin.**—The existence of cholin may be recognized by—(1) physiological and (2) micro-chemical tests. (1) A saline solution of cholin, of cholin hydrochloride, and of the residue obtained from the alcoholic extract of the cerebrospinal fluid and blood of (*a*) animals in which experimental lesions of the central or peripheral nervous system have produced active degeneration, or (*b*) from patients suffering from any form of disease involving active degeneration of the myelin, produces a similar physiological reaction. The reaction is : A temporary fall of blood-pressure after intravenous injection in animals, which is partly cardiac and partly due to dilatation of peripheral bloodvessels. The alkaloid acts directly on the neuro-muscular mechanism of the bloodvessels themselves. Many substances produce this fall of blood-pressure, but, with the exception of spermin, no other substance gives the peculiar result

which follows the injection of a small dose of atropin. Thus, if a saline solution of the alcoholic extract of blood to be tested has already given a fall of blood-pressure, and then a small dose of atropine be administered, the same solution no longer gives a fall, but a rise of blood-pressure, or, at any rate, the fall is abolished. The micro-chemical tests to be recommended are two in number: (*a*) By the addition of iodine solution, thus forming characteristic crystals of periodide of cholin; (*b*) the formation of octohedral crystals of cholin-platino-chloride. Owing to the difficulty of eliminating microscopic traces of potassium salts during the process of extraction of the cholin, the latter test can only be taken when positive to indicate an excess of degenerative products. The iodine test may be thus applied: The blood or cerebrospinal fluid to be tested is mixed with about five times its volume of alcohol, preferably absolute, well shaken, and allowed to stand for twenty-four hours. The alcoholic extract is then filtered off, and evaporated to dryness at a temperature not exceeding 40° C. The extraction with alcohol is again repeated, and after evaporating to dryness the residue is dissolved in a small quantity of 15 per cent. alcohol. A few drops of this solution are filtered on to a slide, and a drop of a solution of iodine in potassium iodide is added. If cholin be present, brownish-black rectangular plates of cholin periodide will be observed to form.

The question of the existence and detection of cholin, as a product of degeneration, in the blood and cerebrospinal fluid, has given rise to a large number of communications during the past few years. The points disputed are—(1) Whether cholin is really present in the blood and cerebrospinal fluid, or whether it may not be some derivative of cholin, or even an organic body of a dissimilar character; and (2) the reliability of the various tests employed for the detection of cholin.

Mott has given considerable attention to this subject, and has noted on many occasions the presence of other bodies of unknown composition in the cerebrospinal fluid in degeneration of the central nervous system. The point, however, requires further elucidation, and as our knowledge of the exact composition of nervous tissue increases, we may be able to ascertain the nature of these products of degeneration. The cerebrospinal fluid is distinctly alkaline (0·12 per cent. in terms of NaOH), and although cholin may be split off from the complex lipoid molecule as the result of nervous destruction, it is possible that it may not be able to exist as cholin in such a medium.

It is of interest to note that by the previously described iodine test, which has been found to be the most reliable, the cerebrospinal fluid obtained comparatively soon after death shows the presence of appreciable quantities of cholin, or some compound from which cholin is easily dissociable.

**Diseases of Nerves.**—It is convenient here to briefly consider the subject of neuritis, for it is to be remembered that parenchymatous neuritis really is a degeneration of spinal motor and sensory neurones, although the effects of the toxic agents in the blood may be only visible in the more remote portion of the neurones—in other words, the extreme portions of the cells farthest away from the nucleus, which is the centre of nutritional activity. "Stocking anæsthesia" of the leg and "glove anæsthesia" of the arms, characteristic of polyneuritis, indicate that the sensory disturbance does not correspond with spinal root segmentation, nor, except in rare instances, with the whole of one or more peripheral nerves, but is dependent upon distance from the trophic and genetic centres, and possibly also upon distance from the heart, since these cases usually present marked impairment of the general circulation. In six fatal cases of polyneuritis examined by Mott, marked changes were present in the cells of the anterior horns and of the posterior spinal ganglia.

True parenchymatous neuritis is toxic in origin, is, for the most part, usually symmetrical, and affects a great many nerves, thus presenting the picture clinically of polyneuritis. It is necessarily associated with some interstitial changes of the vascular and supporting connective tissue, as in all inflammations of other tissues; but the greater part of the interstitial changes are secondary to the degenerative process, especially where this is of rather a chronic nature. The changes in the nerves may resemble those of primary Wallerian degeneration—viz., breaking up of the myelin, proliferation of the sheath of Schwann, alternate swelling and attenuation of the axis cylinder in various places, and in severe cases its rupture and destruction. The general tendency is for the process to start at the periphery—*i.e.*, at the point farthest from the nutritional centre—and spread centrewards. At the same time, changes often occur in the cells of origin of affected fibres similar to those described in the case of a divided nerve. Should these changes in the cells go on till destruction eventuate, it is impossible for regeneration to occur; but anything short of actual destruction admits of repair taking place, provided proper treatment is adopted and the cause of the disease removed. Unfortunately, through the lack of systematic treatment, a complete degeneration of the cells of origin too often occurs, and then the paralysis is necessarily permanent.

Mott has shown that marked chromatolysis of the Betz cells occurs in cases of chronic alcoholic and chronic lead polyneuritis; this change is more marked than can be accounted for by the small amount of degeneration of the pyramidal tracts, and is due to the effect of the poison on the whole system of efferent neurones concerned with reflex and voluntary movements plus the parenchymatous and peripheral interstitial polyneuritis. All the neurones, however, do not undergo total destruction, but only those in which

the nucleus has become extruded. Experience leads one to think that even in severe cases of polyneuritis, recovery may result from continued passive movement of all the joints and massage of the muscles.

**Periaxial Segmental Neuritis.**—In many cases of peripheral neuritis the myelin degeneration is segmental, and limited to one or several internodes in the course of the nerve fibres. Thus, in teased preparations or sections fibres may be seen in which changes in the myelin sheath are only seen at intervals.

Interstitial neuritis is an inflammation affecting mainly the supporting and vascular connective tissue, with all the phenomena of vascular dilatation, diapedesis, slowing of the circulation, tumefaction of the part, etc. Partly owing to toxic action, and partly to local pressure and malnutrition, there may be a rapid loss of the function of the nerve, of a transitory or more or less permanent nature, according as degenerative changes in the nerve fibres are produced or not. It may occur as the result of traumatism or cold, especially if the individual be a victim of gout or rheumatism. Sciatica and Bell's paralysis are common instances of this affection. In anæsthetic leprosy, the interstitial vascular connective tissue is the seat of specific inflammation due to the local presence of emboli of the specific organisms of this disease, and by the use of proper staining methods the organisms may be seen scattered about in the inflammatory exudate.

**Degeneration of the Central Nervous System.**—The methods of studying Wallerian degeneration in the central nervous system are many, but, for our purpose, the following are the most useful: For the present, the spinal cord will be considered, since here the afferent and efferent tracts are very clearly defined. If the posterior roots be cut, or there be a transverse lesion of the spinal cord, it is possible about fourteen days later to recognize definite changes in circumscribed tracts of the spinal cord, especially if the cord be hardened for some weeks in Müller's fluid. If the cord be cut transversely, the degenerated tracts are recognized by their light yellow colour, while the undegenerated tracts are stained brownish-yellow. There is no method equal to that of Marchi for microscopical examination of such specimens. By this method the early changes in the axis cylinders and myelin sheath will be easily observed, and even single degenerated fibres may be followed the whole length of the cord. The healthy fibres are stained a delicate greenish-grey, while, in contrast, the fatty degenerated axis cylinder processes and myelin sheaths are stained black. The method is only applicable while the products of fatty degeneration are present, and at the end of a month, when these have been mostly removed by phagocytic action, it is of very little value.

For degenerations of long standing, the Weigert or Weigert-Pal methods are extremely useful, especially where sclerosis has taken

place. The healthy white matter is stained blue by this method, and the sclerosed tissue is yellow or unstained according to the method adopted. Wallerian degeneration occurs in all organic lesions of the central nervous system. Its distribution will depend entirely upon the position of the ganglion cells destroyed, and the fibres which have been interrupted from continuity with their cells of origin, of which they form an integral part, for it is just as impossible for a nerve fibre to exist when separated from the part of the cell containing the nucleus as it is for the separated portion of a cell of any other known tissue.

The microscopical changes in the fibres as a result of degeneration are a breaking up of the myelin sheath, a swelling of the axis cylinder owing to osmotic changes within it, and a marked fatty degeneration. The clear distinction between the axis cylinder and the myelin sheath is thus rapidly lost. Later, as the phagocytes remove the altered myelin, spaces may be seen with the swollen granular and irregular axis cylinder in the middle. As the absorption of degenerated nervous structures proceeds, the neuroglia cells proliferate, partly owing to the stimulus of degenerative products, and partly simply as a replacement fibrosis, so that eventually neuroglia tissue may entirely take up the place formerly occupied by the essential nervous structures.

The process during the early stages has been one of softening; it is now a true sclerosis, but there is no tendency in uncomplicated primary or secondary degeneration for the sclerosis to progressively extend its limits, and it may be entirely limited to microscopic areas.

## Causes of Disease of the Nervous System.

In order to understand the pathology of nervous diseases, it is highly necessary to consider carefully the causes which lead up to the changes in structure and function observed clinically and in the post-mortem room, and to co-ordinate these one with another.

It is convenient to divide the causes of pathological processes occurring in the nervous system into *intrinsic* (viz., those which are due to either inherited or acquired defect within the neurone itself) and *extrinsic* (viz., those essentially due to the effects produced on the neurone by external agents). It must be remarked, however, that in nearly all cases, except those due to actual injury, the two are always more or less combined.

**Intrinsic Causes.**—Pre-eminent among all the causes of nervous disease stands hereditary predisposition. It may come from the maternal or paternal side, and is then usually spoken of as direct; or, again, hereditary taint may have passed over the immediate parents, and may come from grandparents or more distant ancestors.

In such cases the hereditary influence is said to be atavistic. According to Weissmann's theory of the continuity of the germinal plasm, there is no limit to the remoteness of the origin of a neuropathic taint.

There is a popular notion that the children of parents who are closely related are very prone to inherit neuropathic tendencies. There would seem to be very little foundation for the belief, except in cases where there is already a neuropathic tendency present in the ancestry of such parents. Under these conditions the effects of such a tendency will almost necessarily be cumulative in the offspring, just as they are in the offspring of two unrelated neuropaths. But if such parents have sprung from a healthy stock, there is no evidence to show that unstable nervous systems occur in the offspring of such a union.

Members of neuropathic families may tend to develop the same type of nervous disease, and then the influence is said to be *similar*. In these cases the family history is of extreme value in helping the investigator to give a prognosis when only very early symptoms of disease are present. Instances of *similar heredity* are not at all uncommon, and include such well-known family diseases as Friedreich's ataxia, amaurotic idiocy, hereditary chorea, cerebral diplegia, migraine, optic atrophy, muscular dystrophies, etc.

*Dissimilar heredity* is usually spoken of where there is an inherited neuropathic tendency which exhibits itself in a proneness of the offspring to develop heterogeneous affections of the nervous system with little or no resemblance to those present in the ancestor.

In a healthy nervous system we must suppose that the balance of potential is high, and that the sense of fatigue is the natural indication for sleep and repose by which nervous energy may be recuperated. The neuropath may be conceived to possess in some portion of his nervous system groups and systems of neurones of defective durability, tending early to degenerate—*i.e.*, Friedreich's various forms of idiopathic muscular atrophy, etc. To such conditions Gowers has applied the term *abiotrophic* degenerations.

Again, there may be an inherited low potential readily becoming exhausted, and especially liable to functional depression, thus leading to hysteria and melancholia ; these cases readily undergo premature degeneration under the influence of toxins or stress which would have no effect, or only a temporary one, were the nervous system congenitally healthy.

Again, the biochemical substance, which represents potential, may possess to a high degree inherent chemical instability, and readily fulminate when the appropriate stimulus occurs, thus acting as a centre of discharge of nervous energy, and leading to the occurrence of epilepsy, or, where the instability exists mainly in the highest level of the association systems of Jackson, to a condition of mania, with all its manifestations of excessive functional activity,

since there is depression of the function of highest control, and therefore increased flow of ideas. Similarly, the hereditary tendency to asthma may be due to excessive irritability of the medullary centre, which reflexly gives rise to spasmodic contraction of the bronchioles if any suitable exciting cause be present.

Lastly, there may be some disturbance of the functional relationships of the motor regions of the cortex, leading to disturbance of synergism and the irregular movements so characteristic in hereditary chorea.

Morphologically it must be supposed that there is some defect in the germinal plasm which is concerned in the formation of the neurones.

Acute and chronic alcoholism, syphilis, tuberculosis of the parents, especially at the time of conception, would seem to engender defects in the germinal plasm, thus leading to this neuropathic tendency, and often causing idiocy, imbecility, and dementia. The bearing of syphilis on heredity will be further discussed later when the cause of juvenile tabes and general paralysis is considered.

**Extrinsic Causes** producing morbid changes in the nervous system are dependent upon—(1) Abnormal conditions of the blood and lymph, by which the neurones are poisoned and their metabolism indirectly affected; (2) the existence of abnormal excitation or the presence of deficiency or excess of normal exciting agents.

ABNORMAL CONDITIONS OF THE BLOOD AND LYMPH.—All the cellular elements of the body have as their immediate environment lymph. In the central nervous system, in addition to the perivascular lymph, there is the cerebrospinal fluid, which is mainly secreted by the choroid plexuses. The lymph serves as a middleman between the tissues and the blood, and therefore the underlying causes of an altered cell environment are to be sought in changes in the quantity and quality of the blood-supply.

*Quantity of Blood-Supply.*—An extremely important cause of diseases of the nervous system is a failure in blood-supply to some part of the brain. This question is discussed in dealing with embolism, thrombosis, and cerebral hæmorrhage, in a later chapter. It is important, however, to remember that in conditions of general arterio-capillary fibrosis, associated with high blood-pressure, many of the clinical symptoms seen in some cases, such as headache, loss of memory, and confusion, may be largely due to diminished amount of blood-supply owing to the thickening of the middle and internal coats of the arteries. In these cases, where manifestations of so-called chronic uræmia are present, it is quite impossible to separate the symptoms due to failure in elimination of toxic products, and those actually due to the circulatory disturbance *per se*.

Again, it is important to remember that, in conditions of high blood-pressure, unless the cerebral vessels are actually contracted

and sclerosed, there is engorgement of cerebral vessels, since the general vasomotor spasm present all over the body is not present in cerebral vessels, which are much less under the control of the vasomotor system than vessels elsewhere in the body. Hence, the cerebral vessels are largely at the mercy of the general circulation, and become engorged when contraction of the general arterial tree occurs, and are, on the contrary, largely emptied where the general arterial tree is dilated, as in conditions of shock and collapse, with resulting cerebral anæmia. Any sudden failure of cerebral circulation induces syncope, as seen so frequently in conditions of heart failure.

*Quality of Blood-Supply.*—Deficiency of oxygen, due to anæmia, leads to functional depression, loss of power of attention, lassitude, and mental fatigue. Impoverishment of the blood in women, by frequent pregnancies and excessive lactation, causes neuralgia, nervous exhaustion, and in neuropathic subjects hysteria, neurasthenia, and melancholia. Probably there is an alteration in the constitution of the blood due to auto-intoxication, or a "submininal" deficiency of some important constituent of the blood may be the cause of morbid nervous phenomena. The most striking example of the effect of absence or "submininal" deficiency of a normal constituent of the blood upon mental and bodily development is absence of development or premature atrophy of the thyroid gland. A cretinous idiot, with or without diplegic manifestations, is the result in the former case; myxœdema, with all its train of mental symptoms, is the result in the latter case. Proof of this is given in the rapid improvement and development of cretins if they be recognized early, and treatment with thyroid extract be continued throughout life. Even more striking is the proof in cases of adult myxœdema, where all symptoms will rapidly disappear if the deficiency be made up by administering the gland by the mouth. Such conditions as acromegaly and diabetes, associated with morbid changes in the pituitary gland and pancreas respectively, only secondarily affect the nervous system. Defects of necessary constituents are of minor importance, however, compared with the toxic causes of disease of the nervous system.

(*a*) *Excess of Normal Constituents in the Blood.*—Carbonic acid, nitrogenous waste products, and altered lipoids, may be given as instances of normal by-products of metabolism, which, if present in excess, will undoubtedly give rise to symptoms of disease and functional derangement of the nervous system.

Again, many of the symptoms of such a condition as Graves' disease—viz., palpitation, fine tremors, vasomotor irritability, and increased mental excitability—are mainly due to the escape of excess of thyroid secretion into the blood, since all of the above-mentioned symptoms may be readily produced by administering excess of thyroid extract either by the mouth or subcutaneously.

(*b*) *The Presence in the Blood of Abnormal Constituents* is by far the most important extrinsic cause of nervous disease, and the subject may be considered under the following headings: (1) Poisons produced within the body by perverted function of the tissues of one or more organs (auto-intoxication), or by the action of micro-organisms upon the living tissues and body fluids; (2) poisons introduced from without.

1. Poisons produced within the Body: Perhaps the best example of auto-intoxication affecting the nervous system is furnished by uræmia, the nervous manifestations of which are severe headache, drowsiness or coma, and epileptiform convulsions, and occasionally symptoms of polyneuritis. In this condition there is always marked renal inadequacy and increase of uric acid and other injurious by-products of general metabolism in the blood; so that any slight exciting cause, such as constipation or slight gastro-intestinal catarrh, may upset the already overtaxed functions of the liver, and lead to just a sufficient increase of toxic waste products in the circulation to precipitate an attack of uræmia.

Diabetes (a result of imperfect carbohydrate metabolism) may cause multiple neuritis and coma, with associated symptoms of air-hunger (hyperpnœa). According to Pavy, the mounting up of carbon dioxide in the tissues owing to the lessened alkalinity, and therefore lessened carbon dioxide carrying-power, of the blood, is an important factor in the causation of both the coma, and symptoms of air-hunger associated with it. The experiments of Beddard, Pembrey, and Spriggs, however, have shown that the blood in diabetic coma and in the precomatose stage, can combine with considerably more carbon dioxide than it actually contains, and that, therefore, the above view of Pavy is untenable. They contend that the symptoms of air-hunger are caused by the increasing concentration of unneutralized acid substance. The decreased reactivity of the protoplasm of the nerve cells of the medulla, due to the prolonged acidosis, renders their reaction more easily disturbed by, and therefore makes them more sensitive to, the stimulating influence of any acid body, including carbon dioxide and other acids produced during metabolism. Similar changes, they suggest, will be taking place in all the other cells of the body, and as the acidosis increases, the metabolic activity of the tissues is thereby slowly and progressively diminished until consciousness, and finally life, is no longer possible. This view is in accord with that favoured by continental authorities—namely, that the cells of the body, owing to the increasing acidosis and the deprivation of alkali, are unable to carry on their usual oxidation processes.

*Cholæmia*, resulting from obstructive jaundice, may be attended by stupor and marked psychical depression. Again, the rapidly fatal results attending acute *yellow atrophy of the liver*, the profound changes in the urine and blood, the jaundice accompanied by motor

irritability, delirium, delusions, stupor and coma, attest the extreme importance of the liver in maintaining the normal quality of the blood.

In *pernicious anæmia* and other grave anæmias, degenerative changes in the spinal cord of the nature of a subacute combined sclerosis occur not infrequently, and are probably due, not so much to the deficiency of oxygen (which is necessarily associated with the great destruction and lack of production of red corpuscles), as to the same toxic substance which brings about the grave anæmia. Again, owing to the deficient oxidization of waste products of metabolism, there may arise an auto-intoxication, which may be an important factor in determining the degeneration. In some cases of pernicious anæmia it is possible to determine a probable infective cause of the disease, where, for instance, a marked pyorrhœa alveolaris is present.

Examples of poisons due directly or indirectly to micro-organisms occur in many infective diseases—*e.g.*, typhoid fever, typhus, small-pox, scarlet fever, influenza, pneumonia, septicæmia, tuberculosis, rheumatism. Delirium is a frequent complication during the acute stages of these diseases, and is probably due to the combination of high temperature and the toxins present in the lymph. In severe cases stupor, and even coma, may occur, going on to death; and it has been shown that in this stage the nerve cells of the brain and spinal cord undergo an acute morbid biochemical change (see Plate II., Fig. 11). It has been shown that one of the neuroglobulins actually is precipitated at a temperature corresponding to 109° F., so that in some cases death in hyperpyrexia may be due to this cause. These particular poisons have not a selective action on any special part of the nervous system, but nevertheless many cases of neurasthenia, insanity, and neuritis, date from an attack of an acute specific fever. The toxins of the rheumatic organism are especially liable to produce, or be followed by, hyperpyrexia and chorea, thus indicating a selective action on the cells of the cortex cerebri. Payne and Poynton claim to have isolated the organism of rheumatism from the cerebral cortex of several cases of chorea gravis which have died in the acute stage. Experiments by Homon, Orr, and Rows, indicate that microbic toxins may pass up the lymphatics of nerves, and by the posterior roots gain entrance to the spinal cord, and cause degeneration in the posterior columns.

In cerebrospinal meningitis, posterior basic meningitis, acute delirious mania, leprous neuritis, and possibly chorea, the inflammation of the enclosing and supporting structures is due to the local multiplication therein of the specific organism. In syphilis of the nervous system, probably the *Treponema pallidum* is always present in the local lesions attacking the enclosing, supporting, and vascular tissues of the brain and spinal cord, although in these cases the organism has not been demonstrated.

Undoubtedly some toxins have a selective action on particular parts of the nervous system.

The syphilitic virus, when it attacks the supporting, enclosing, and nutrient vascular mesoblastic tissues, shows a marked disposition to affect structures about the base of the brain. Thus, paralyses of the sixth and third nerve are common as the result of manifestations of active syphilis.

In *rabies*, although the whole nervous system is charged with the poison, the symptoms show that the medulla oblongata is specially affected. Moreover, whether we regard the "negri bodies" constantly found in rabies as a specific protozoon undergoing its life-cycle in the cells of the nervous system, or look upon these bodies as endocellular degenerative products, caused by the specific virus of rabies, it is nevertheless true that the cells in the hippocampal region of the brain and the medulla never fail to show these bodies in the case of rabies. Seeing that the saliva is the infective agent, it is remarkable that the parts of the brain presiding over taste and smell should be the seat of special affection in the nervous system.

*Tetanus*, again, is an extremely interesting instance of the selective action of the tetanus toxin. It would seem that the action of the toxin, like that of strychnine, is mainly confined to the synapses of the reflex arcs of the spinal cord and brain stem. The resistance of all these synapses is greatly reduced, and reciprocal innervation is entirely upset, so that impulses passing down the pyramidal tract, either as the result of electrical stimulation of the Rolandic cortex experimentally, or owing to definite voluntary attempt at movement in a patient the victim of tetanus, result not in the attempted flexion, but in an extensor spasm, since the extensors are on the whole more strongly stimulated as the result of a lowering of the spinal resistance. In all cases in which the main flow of afferent energy is diverted to the efferent side through the two lower arcs of the central nervous system, a variable amount of extensor rigidity results.

It would seem to be probable that both tetano-toxin and strychnine lower the synaptic resistance, especially through the basal nuclear and cerebellar arcs, since mental disturbance is very slight and unobtrusive; while the general muscular hypertonus, with extension of the limbs and closure of the jaws, suggests strongly that seen in decerebrate rigidity, where all afferent impulses are now shunted through Deiters' and the red nucleus, since the path to and from the cerebral cortex is no longer present. Again, extensor movements are not so easily obtained from the cerebral cortex on stimulation, while the flexor movements are much more widely represented. Similarly, it is almost impossible to obtain closure of the jaws by cortical stimulation normally, while opening of the jaws is obtained from a comparatively large area.

All these facts point strongly to the view that in tetanus and strychnine-poisoning there is a great lowering of synaptic resistance in the spinal cord and brain stem. Thus, the main mass of afferent impulses would pass by the way of least resistance through the lower arcs, never reaching the cerebral cortex, with the net result that, per unit of time, the anterior horn cells would receive infinitely more impulses through Deiters' efferent spinal tract and the pre-pyramidal tract (rubro-spinal) than under normal conditions. These would necessarily pass to the general musculature, thus giving rise to a condition of hypertonus resembling largely that in decerebrate rigidity. This result is extremely well exemplified in the tonic closure of the jaws (lockjaw), a constant symptom of this disease. Here the resistance at the synapses around the motor cells of the fifth nerve nucleus is so reduced that in any voluntary attempt to open the mouth there is no reciprocal inhibition of the fifth nerve muscles, because, according to McDougall's drainage theory, the pyramidal impulse then flows by the way of least synaptic resistance, and this, owing to the selective action of the toxin, is at the fifth nerve nuclear synapses; hence, any attempt at opening the mouth can necessarily only increase the force of closure, which is constantly the case in this disease.

Tetanus toxin would seem to travel to the spinal cord from the seat of infection largely by the axon of the nerves in the immediate neighbourhood, and the limb which is the seat of infection is, accordingly, the first to become affected with the spasms so typical of the disease. There are, however, very soon after signs of involvement of the fifth nerve synapses in the majority of cases.

The strong affinity of the tetanus toxin for the side-chains of nerve tissue is shown by the fact that tetanus toxin, previously mixed with an emulsion of nervous tissue, is quite innocuous in doses which would otherwise rapidly prove fatal.

In cases which have died of tetanus, some authorities have found marked biochemical and biophysical changes in the nuclei and cell bodies of the large motor cells of the cortex and spinal cord.

Another example is offered by *diphtheria*. A neurotoxine is produced by the local action of the bacilli, the effects of which are occasionally shown by the paralysis of the soft palate, paralysis of the muscles of accommodation, weakness and inco-ordination of the limbs (which may amount to paralysis), absence of knee-jerks, and often cutaneous anæsthesia; and the disease occasionally terminates fatally by vagal paralysis, with respiratory or cardiac failure, the lesion being in the majority of cases of the nature of a peripheral neuritis.

2. Poisons introduced from Without: One of the most widespread and potent causes of nervous and mental disease is the abuse of alcoholic stimulants. The action of alcohol is highly idiosyncratic, and to persons with unstable nervous systems a small quantity of

alcohol acts as a poison. In all persons overdoses may give rise to coma, with dilated pupils and general muscular flaccidity.

The result of chronic inebriety may be acute delirium with fine general muscular tremor, and visual hallucinations of a horrible character. This acute form of alcoholic poisoning — *delirium tremens*—is much more common in men than in women, and it is very remarkable how a serious accident or illness, such as pneumonia, will bring on an attack in a person addicted to alcoholic intemperance, even though he may not have indulged himself for days or weeks before his accident or illness.

Alcohol acts especially on the higher centres, and a drunken man may exhibit "the abstract and brief chronicle of insanity, going through its successive phases in a brief period of time" (Maudsley). The functions of the brain are stripped away successively in an inverse order to their development—viz., moral control and responsibility, judgment and deliberation, attention and concentration, memory and receptivity. The effect on the brain of chronic drinking may be dementia, very characteristic features of the mental degradation being disorientation in time and place, personal illusions, and loss of memory, especially for recent events, thus indicating a failure of receptivity and of the formation of memory pictures in the higher centres. This alcoholic dementia, termed "Korsakow's psychosis," is much commoner in women than in men. The frequency with which this disease occurs in women, especially married women, as compared with men, may be due, as Mott has suggested, to associated microbial intoxication arising from endometritis, parametritis, and salpingitis. Moreover, the frequency with which this psychosis is accompanied by delusions of a child being in the bed may have some relation thereto.

The improvement which generally takes place (except in advanced cases in dementia) when all alcohol is prohibited, shows that the poison has damaged, but not destroyed, the nervous elements.

In addition to, or apart from, the mental symptoms of alcoholism, there are frequently sensory disturbances and motor paralyses as the result of polyneuritis, affecting specially the lower limbs, although the upper limbs, respiratory and cardiac and gastro-intestinal musculature, are not infrequently affected in severe cases, thus causing feeble, irregular, and rapid respiration and cardiac action, and much digestive disturbance and constipation.

Lead is peculiar in selecting the nerve which supplies the extensor muscles of the wrist and fingers, so that *dropped wrist* is almost characteristic of this form of toxic neuritis. Lead is also occasionally responsible for a form of chronic inflammation of the cerebral cortex (encephalitis saturnina), which gives rise to a symptom-complex—viz., dementia, loss of memory, weakened intellect, tremors, paresis and epileptiform seizures, hallucinations of sight and hearing, and mental exaltation or depression.

Arsenic has a selective action on the peripheral nerves, giving rise to a widespread polyneuritis, which usually affects all four limbs. Sometimes psychical disturbances arise, and rarely epilepsy.

Workmen in india-rubber factories not infrequently suffer from severe mental disturbance and polyneuritis as the result of inhalation of the fumes of bisulphide of carbon.

As a result of carbon monoxide poisoning, symptoms of grave disturbance within the central nervous system occur. There may be every degree of dulling of sensibility from slight stupor to deep coma, associated with respiratory changes, the breathing often being Cheyne-Stokes in character, and respiration may stop some little time before the heart ceases to beat. The post-mortem appearance of the central nervous system is very characteristic. Enormous numbers of small capillary hæmorrhages are observed throughout the cerebral cortex and in the corpus callosum and basal ganglia, and to a lesser extent in the brain stem. Microscopically, the cells throughout the cortex show various chromatolytic changes, and there is present a widespread fatty degeneration of the endothelial cells of the small bloodvessels. In some cases examined at Claybury, the chromatolytic changes in the cells of the nuclei of the vagus were much more marked than those in the other cranial nerves. Hence, the effect of the somewhat selective action of the poison and lack of oxygen on these nuclei may partly explain the disturbances of respiration so common in these cases.

There are a number of other poisons besides alcohol which, habitually taken into the body, produce grave effects on the central and peripheral nervous system—viz., absinthe, ether, cocaine, opium, morphia, hashish, and tobacco. Various characteristic mental symptoms arise, and in the case of absinthe epilepsy is not an infrequent complication.

Beri-beri, or kakke, which is associated with polyneuritis, and occurs in Eastern countries, would seem to be mainly due to the continued consumption of unsound, mouldy rice, which cereal is the most important food-stuff of the yellow race.

The characteristic lethargy of sleeping sickness is due to a chronic meningo-encephalitis caused by the presence in the blood and cerebrospinal fluid of the *Trypanosoma Gambiense*. A fly, the *Glossina palpalis*, acts as the carrier and intermediate host.

Pellagra is an affection of the skin associated with degenerative changes in the brain and spinal cord. These changes and the associated toxins cause a fatuous melancholia, often with suicidal tendencies, and more rarely mania. It is supposed that this disease is due to the consumption of bad maize containing some toxic substance, possibly a fungus (*Oosporon Maidii*).

Ergotism is a disease due to the consumption of bread made from rye which has been infected with the *Claviceps purpuræa*. The poison thus introduced produces progressive degenerative changes in the brain and spinal cord.

DEFICIENCY OR EXCESS OF NORMAL STIMULATION.—Structure and function are reciprocal and mutually interdependent. A structure which is not used will gradually lose its function, while its nutrition will also suffer, and atrophy will gradually occur. Amputation of a limb, especially in early life, leads to atrophy of the nervous structures which presided over the sensation and movement of the part. This is seen in both the grey and white matter of the spinal cord of the same side. Again, as an instance of mutual interdependency may be cited the fact that, where there is congenital absence of one side of the cerebellum, the opposite frontal lobe, which is so closely connected with it functionally and anatomically, is found at post-mortem examination to be small and undeveloped also. A function not used will gradually disappear, and become increasingly more difficult to evoke. This fact is of great importance in functional neuroses and psychoses—*e.g.*, hysterical paralysis and melancholia—because the longer a mental or bodily function remains in abeyance, the more likely is the defect to become permanent. The converse is equally true: the longer a perverted function is in existence, the more likely is it to become permanent, and the more unlikely is it to disappear under treatment. Thus, auditory hallucinations—a very important and frequent symptom in the insane—usually commence with indistinct noises. These are followed by voices, which may eventually become so distinct and systematized that the patient's whole psychical existence is taken up and determined by these abnormal stimuli from within. This illustrates the progressive strengthening and fixation of the perverse function of the mind, and the progressive weakening and dissolution of the normal functions.

ABNORMAL STIMULI FROM WITHOUT—1. *Psychical Stimuli.*—Mental pain in the form of grief, worry, anxiety, fright and shock, violent emotions (pleasurable or painful), sexual excesses or perversions, and excessive brain work in persons with a neuropathic taint or inheritance, frequently precede and are the immediate exciting cause of various forms (1) of psychoses—*e.g.*, mania, melancholia, delusional insanity; (2) of neuroses, tics, hysteria, epilepsy, hystero-epilepsy; (3) of organic brain disease—*e.g.*, apoplexy, thrombosis, general paralysis. Stress and overexertion physically may often be observed in practice as determining and auxiliary causes in bringing about neuritis and degenerative processes of the central nervous system. The most striking examples of *psycho-motor functional paralyses* from stress are furnished by writers', pianoforte-players', violinists', and typewriters' cramp, and hammerman's palsy.

Patients suffering from exhaustion psychoses usually present very extensive peripheral anæsthesia and analgesia involving the arms and legs, and more or less of the trunk. Such patients may complain bitterly and continuously of pain referred to the non-æsthetic area, which would seem to dominate the consciousness, and by the

law of contrasts to be rendered spontaneously painful and hyperæsthetic, thus illustrating one possible effect of the loss of appreciation of general afferent impulses from the periphery.

2. *Physical Stimuli.*—Visceral reflex irritation may not infrequently act as an exciting cause of neuroses and psychoses in neuropathic subjects. Thus, intestinal worms, teething, and digestive disturbances, not infrequently produce in infants or rickety children convulsions and spasm of the glottis. But in the majority of these cases the absorption of some toxin into the blood-stream is associated with the peripheral irritation. Various functional and organic diseases of the female reproductive organs act as exciting causes in the production of hysteria, hystero-epilepsy, melancholia, and mania. Moreover, paroxysmal attacks in these diseases are more liable to occur at the menstrual period or the menopause. Again, apart from any definite signs of infection, childbirth is not infrequently followed by various psychoses in persons with unstable nervous systems.

Trigeminal neuralgia may be produced by the irritation of a carious tooth. Wax in the ear may lead to vertigo and tinnitus aurium, and even excite epileptic fits in a person with an inherent epileptic tendency, or the subject of epilepsy. Many examples of peripheral disturbances may be cited as exciting causes of nervous affections; for example, irritation of the terminals of the vagus in almost any part of its widespread visceral distribution may lead to reflex vomiting. Among the numerous examples of referred pain may be cited the characteristic pain of angina pectoris which radiates down the inner side of the left arm. This is to be explained by the origin of the cardiac branches of the sympathetic from the same segment of the spinal cord as that from which the sensory branches of the ulnar nerve arise, and, according to a physiological law, depending upon morphological conditions, the mind refers the pain to a definite area of skin, and this pain is termed "a referred pain." The viscero-vascular structures are supplied by the fibres of the white and grey rami of the sympathetic, and strong irritation of internal visceral structures produces intense impulses, which are carried by afferent visceral fibres into the grey matter of the various segmental metameres of the spinal cord; these, by radiation, excite the neurones, which receive painful stimuli from the associated skin areas. The result is twofold, the establishment of a protective reflex, by contraction of the correlative skeletal muscles, and a painful sensation, transmitted to the seat of consciousness, especially increased if this protective reflex is broken down voluntarily or involuntarily. The mind is only cognizant by the senses of this particular painful stimulus coming from a definite skin area; it therefore refers the pain to it. Thus, by the establishment of the protective reflex, the parts are kept as much at rest as possible. The severe pain accompanying it

may, as Sherrington aptly says, be looked upon "as a psychical adjunct of this protective reflex." The pain is, however, much greater in some individuals than others, not because the stimulus is greater, but because the subjective mental attitude of the individual, by a concentration of consciousness to the painful spot, is greater. But it might logically be asked, Would it be possible to concentrate the attention on a viscus of which one has no knowledge by touch or sight, if it were not for the pain referred to the correlated skin area? By no effort of the attention can we imagine the rhythmical contractions which are taking place with phasic or periodic regularity in our ureters, bile-ducts, and gall-bladders. It is only when they contract violently in response to intense irritation that we are painfully instructed, by experience and the referred pain, as to the cause.

A great deal of discussion has arisen as to whether pain can be felt in the viscera. There can be no doubt that a peculiar dragging and sinking sensation is associated with irritation of the viscera, probably due to stimulation of coarse afferent fibres with Pacinian corpuscles, independent of the sensation in the skin areas. Many patients who suffer with gastric crises complain of a deep-seated pain within the abdomen, and no doubt this is due to irritation of the splanchnic afferent neurones, which are undergoing destruction in the posterior roots of the mid-thoracic segments.

Cases often attend hospitals for gastric troubles which are thought to be dyspepsia, whereas really they are very mild gastric crises. In severe cases there is no doubt intense irritation, generally with destruction of the sixth, seventh, and eighth posterior roots, conveying cutaneous splanchnic impressions from the stomach.

The quality of a sensation depends on multiple circumstances—the nature and intensity of the peripheral excitation, the state of the conducting neurones and of the cortical perceptive centres—but whatever be the cause of the objective sensation coming from the periphery, it is in the cortical terminus of the afferent system that the stimulus is perceived as a state of sensation of heat, cold, pain, contact, or movement, and localized to a particular part of the body. The localization is very often imperfect; this is explicable by the fact that each spinal segment of the grey matter of the posterior horns is correlated with a definite skin area. When all the sensory cutaneous neurones proceeding directly to that area have been destroyed, sensory impulses may still enter the cord, owing to the overlapping of adjacent roots in the nervous supply of that skin area, and the stimulus be referred to an area above or below. In the limbs, where the segmented character is obscured, the cause of this imperfect localization is not so obvious. The wrong localization is, however, due to a state of consciousness brought about by excitation of neurones in the wrong segment, and consequently is outwardly projected in the mind to that area of skin

which is morphologically correlated with the segment excited. Another excellent instance of this condition is the tenderness on pressure and rigidity of muscle in the region of the epigastrium which is so uniformly associated with gastric ulcer. When ulceration of the stomach occurs, the sympathetic nerve terminals will necessarily be exposed and highly irritated by the acid digestive fluids within the viscus, and a stream of intense exciting afferent impulses thus set up may conceivably produce an intense excitation of the grey matter of the posterior horns of the spinal segments with which the white rami communicantes are connected. But these same segments also contain pain receptors of fibres proceeding from definite skin areas, and the mind, having no consciousness of localization of painful impressions from internal organs, refers the pain to the corresponding skin area of the spinal segments excited. Similarly, the tenderness of the muscles on pressure, and the hyperæsthesia of skin, would be explained by the passage of impulses, brought about by a peripheral stimulus which normally would not produce pain, through an irritated posterior root or spinal segment, since the brain, having no consciousness of the viscus, would necessarily interpret these impulses as being due to local affection of the skin and muscle nerves themselves. Again, the local muscular rigidity might be explained by a lowering of synaptic resistance round the anterior horn cells of the same segment, due to the passage to them through the collateral fibres of an excess of afferent stimuli. Such lowering of the synaptic resistance would lead to increased tonus of the muscle or part of a muscle supplied by those anterior horn cells, owing to a drainage of neighbouring cells of tonic impulses which constantly pass down by the rubro-spinal and vestibulo-spinal tracts to maintain normal tonus.

**Effects of Degeneration on Function.**—In order to understand this subject, it is necessary to discuss briefly the architectural mechanism of the nervous system. Considering first the afferent system, it will be remembered that it was pointed out, in connection with the discussion of the symptoms following the section of a peripheral nerve, that the peripheral nerve distribution does not in any way correspond with the root distribution in the limbs. This fact is of considerable importance, since the distribution of the sensory loss will often be sufficient to determine the position of the pathological lesion—*i.e.*, whether it is of posterior root or peripheral nerve origin.

Afferent impulses reach the spinal cord by means of the posterior roots from both the superficial and deep parts of the body, including the viscera, each segment being connected with a posterior spinal ganglion, from which it receives fine and coarse fibres. The former are connected with superficial cutaneous structures, and the latter with deep structures—*e.g.*, joints, bones, muscles, tendons. The fine fibres end in the grey matter of the posterior horn of the same

segment—Lissauer's tract—and form the afferent path of the reflex arc in the superficial skin reflexes. The coarse fibres arising from afferent neurones innervating the deep structures are of three kinds: (1) Short, spinal; (2) medium length, cerebellar; (3) spino-bulbar. The short spinal fibres, after passing through the posterior column, enter the grey matter at the base of the posterior horn *via* the root zone, and form the afferent path for the segmental deep reflexes. The medium length cerebellar fibres run up through several segments in the postero-external column and arborize round the cells of Clarke's column; they connect with the system of afferent spinal cerebellar neurones. The spino-bulbar are long fibres, which form the columns of Goll and Burdach. The transmission of impulses from the periphery to the brain is therefore extensively conducted by long fibres in the white matter of the spinal cord, and these afferent groups are composed of—(1) Afferent fibres of the posterior columns forming the first segments of the cerebellar afferent system; (2) ascending fibres, traversing the periphery of the lateral columns and forming two groups: (*a*) antero-lateral, or Gower's tract, consisting mainly of crossed fibres, which have three terminal stations—the majority go to the valve of Vieussens and the vermis of the cerebellum, a few end in the lateral nucleus, some end in the corpora quadrigemina, and a very few end in the pulvinar of the optic thalamus; (*b*) direct cerebellar, which pass into the restiform body and the inferior peduncle, to end in the vermis.

The *superficial* sensory proto-neurones, after entering the grey matter of the posterior horns, terminate in branching processes which come into physiological contact with the processes of the cells in the neighbourhood of the base of the posterior horns. Separate groups of these cells in each segment form definite receptors for the different superficial sensations of touch, pain, heat, and cold. However, a certain number of these proto-neurones, which seem to be closely connected with the power of discriminating two points, pass directly up the posterior columns to receptors in the gracilis and cuneate nuclei (Fig. 5).

Similarly, the *deep* sensory proto-neurones pass to specialized receptor cells. A considerable number of these, conveying impulses from the muscles, bones, and joints, pass directly up the posterior columns of the same side to relays in the gracilis and cuneate nuclei. Others pass to and break up round the specific receptors for pain and touch. Collaterals also arborize round the cells of Clarke's column, and some break up round the corresponding anterior horn cells.

The diagram illustrates the fact that fibres arising from these specific receptors pass more or less rapidly to the other side of the cord, leaving the grey matter, and passing up in the white matter. Those conveying painful and thermal impulses cross the spinal cord, and pass upwards in the antero-lateral column among the fibres of

the antero-lateral tract. On the other hand, there is an alternative path for tactile impulses, since they may either cross the cord and ascend in a secondary sensory neurone passing up the anterior ground bundle, or they may ascend by a primary sensory neurone in the posterior column of the same side of the chord. These fibres conveying tactile impulses are, however, constantly relaying in the grey matter round the tactile receptors after a comparatively short

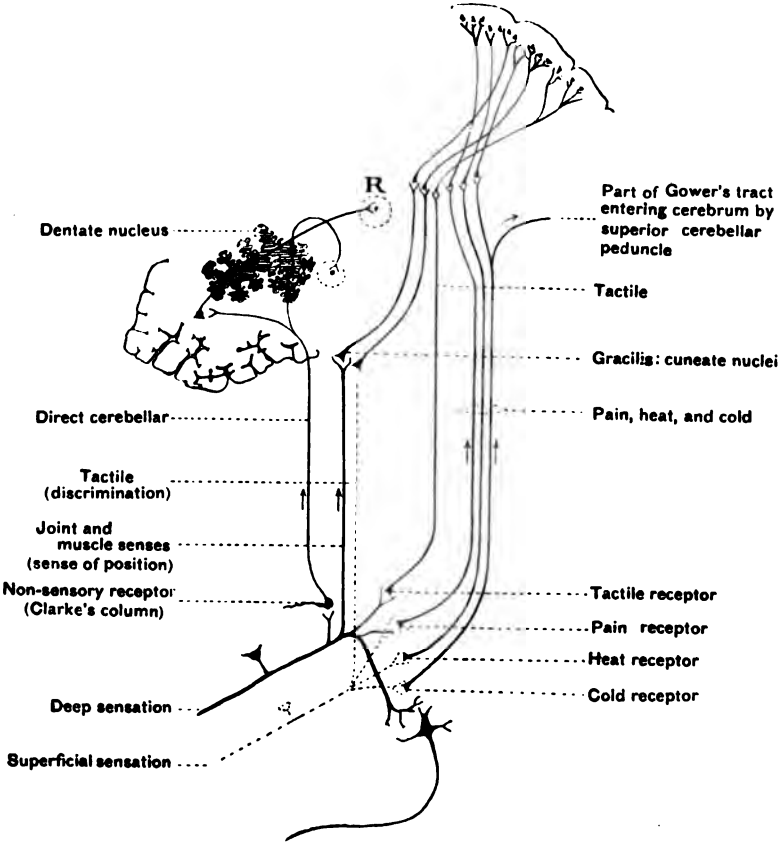


FIG. 5.—DIAGRAM TO ILLUSTRATE AFFERENT SYSTEMS TO CEREBRUM AND CEREBELLUM.

course in the posterior columns, and crossing to the opposite anterior ground bundle, so that by the time tactile impulses from the lower limbs have reached the upper cervical region, it is probable that they have all crossed to the opposite side of the cord. Impulses for tactile discrimination and sense of position traverse the whole length of the cord on the same side in the posterior columns, finally relaying in the gracilis and cuneate nuclei, and crossing to the

opposite side in the superior sensory decussation in the medulla. The non-sensory afferent impulses concerned with the functions of equilibrium are conveyed by fibres arising from the cells of Clarke's column, and pass up the direct cerebellar tract of the same side of the cord to the cerebellum, which they enter by the inferior cerebellar peduncle. These tracts conveying impulses from the specific receptors of the cord remain quite distinct, and more or less widely separated during their passage through the medulla and pons Varolii; and it is only in the mesencephalon, just before the thalamus is reached, that they become combined, and here only is it possible for a comparatively small lesion to give rise to complete loss of all sensations over the opposite side of the body.

These secondary sensory neurones, after traversing the mesencephalon as a combined bundle, enter the optic thalamus, where they arborize around cells from which arise the tertiary sensory neurones which pass to the cerebral cortex after subdividing in the subcortical tissue. Many finally terminate round the cells of the ascending frontal convolution, while the majority terminate round the cells of the ascending parietal convolution.

In partial lesions of the posterior roots or peripheral nerves, the fibres conveying impulses from either the superficial or deep parts may be affected separately. From the above brief survey of the afferent system, it will be readily understood that in such cases, where superficial sensation alone is abolished, the patient will still be able to appreciate pressure as opposed to pure touch, pain or excessive pressure, and that he will be able to form an accurate conception of the passive position of his joints and of active movements of his muscles, while localization of pressure is very inaccurate. On the other hand, where deep sensation alone is abolished, as is the case in some early cases of tabes, and in more or less rare cases of peripheral neuritis, superficial touch, pain, thermal sensations, and cutaneous localization, are intact, while pain on excessive pressure, recognition of passive position of joints, and the other phenomena depending on the integrity of the deep sensation, are in abeyance. In cases where a lesion in the cord affects the secondary sensory neurones, it is usually found that painful sensibility and thermal sensibility are lost together, owing to the contiguity in the cord of the tracts conveying the impulses for these sensations; yet it is not infrequently observed that analgesia exists without corresponding thermo-anæsthesia, and in rare cases sensibility to heat may even be abolished without coincident loss of cold sensibility. In contradistinction to partial peripheral lesions, sensibility to all kinds of pain, both superficial and deep, is equally affected, although at the same time non-painful pressure and its gradual increase can be readily appreciated. Thus, cutaneous painful impulses and those arriving by the deep nerves become combined in the pain receptors of the cord, and

part company with all other impulses arriving by the superficial and deep sets of nerves. When sensibility to heat or cold is disturbed as the result of a cord lesion, there is no differentiation between loss of sensibility to minor differences of temperature and extreme degrees of temperature, as is not infrequently the case in peripheral lesions.

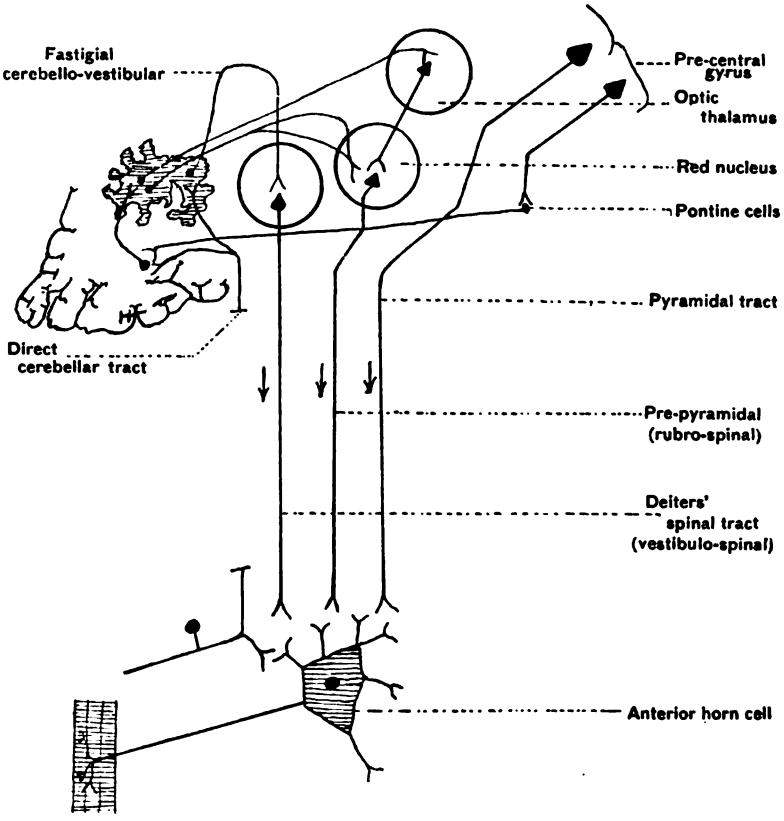


FIG. 6.—DIAGRAM TO ILLUSTRATE THE VARIOUS PATHS OF TRANSMISSION FROM THE BRAIN TO THE SPINAL MOTOR NEURONES.

The spinal cord serves also as an organ of transmission of efferent impulses from the brain to the periphery (Fig. 6). The cells of origin of these neurones are situated above the spinal cord. This afferent or descending system is composed of (1) cortico-spinal fibres, (2) vestibulo-spinal, (3) rubro-spinal, (4) tecto-spinal, (5) posterior longitudinal bundle fibres. The cortico-spinal system commences in the large Betz cells situate in the grey matter of the ascending frontal convolution. These cells give origin to the

crossed and direct pyramidal tract. The vestibulo-spinal (bulbo-spinal) nerve ends in a mass of grey matter in the floor of the bulb, known as Deiters' nucleus, the vestibular nucleus, or the nucleus of Bechterew. From this nucleus fibres pass down the antero-lateral column to end, by arborization, around all the spinal motor neurones. Fibres also pass into the posterior longitudinal bundle, to end in the ocular nuclei. The term "vestibulo-spinal" is given to these fibres, because they convey impressions from the semicircular canals to the cervical, dorsal, lumbar, and sacral spinal motor neurones of the same side (*vide* Fig. 6). These vestibular impressions play an important part in the maintenance of the spinal tonus of muscles.

**Rubro-Spinal (Mesencephalo-Spinal).**—The most numerous and important set of mesencephalic fibres arise from the red nucleus. After decussation (*vide* Fig. 6) they pass down the lateral column of the cord and arborize at the base of the anterior horn. There is also another system of fibres which belong to the posterior longitudinal bundle, and which have their cells of origin in a mass of grey matter near the posterior commissure. According to Van Gehuchten, the upper connections of these two masses of grey matter are in direct or indirect connection with the optic fibre. These mesencephalo-spinal bundles of fibres transmit to the spinal motor neurones excitations from the optic tract, and help to maintain tonus (*vide* Fig. 6).

**Tecto-Spinal.**—A system of fibres arises in the corpora quadrigemina; some of these can be followed to the sacral region, and it is surmised that they may exercise control over the bladder and rectum.

**Transverse Lesions of the Spinal Cord.**—If the spinal cord be transected, degeneration of the afferent tracts above the lesion will occur. In the case of the long fibres of the posterior columns, this degeneration can be traced as far as the nucleus gracilis and nucleus cuneatus in the bulb. These fibres convey respectively kinæsthetic impulses from the lower limbs and trunk, the upper limbs, trunk, and neck. In addition to these long fibres, there are also fibres pursuing but a short course in the posterior column; these end by arborization around the cells of Clarke's column, which appears first at the second lumbar segment. The fibres, which enter at a lower level, must therefore run upwards in the postero-external column before they end around the cells of Clarke's column. In the lateral columns the fibres which show ascending degeneration are the ventral and dorsal cerebellar tracts. The former consist mainly of crossed fibres, the latter of direct fibres; they are formed by the axons of the cells of Clarke's column.

Transection of the cord in the cervical and upper dorsal region will cause degeneration of the descending fibres in the direct and crossed pyramidal tracts, and also of the fibres of the rubro-spinal

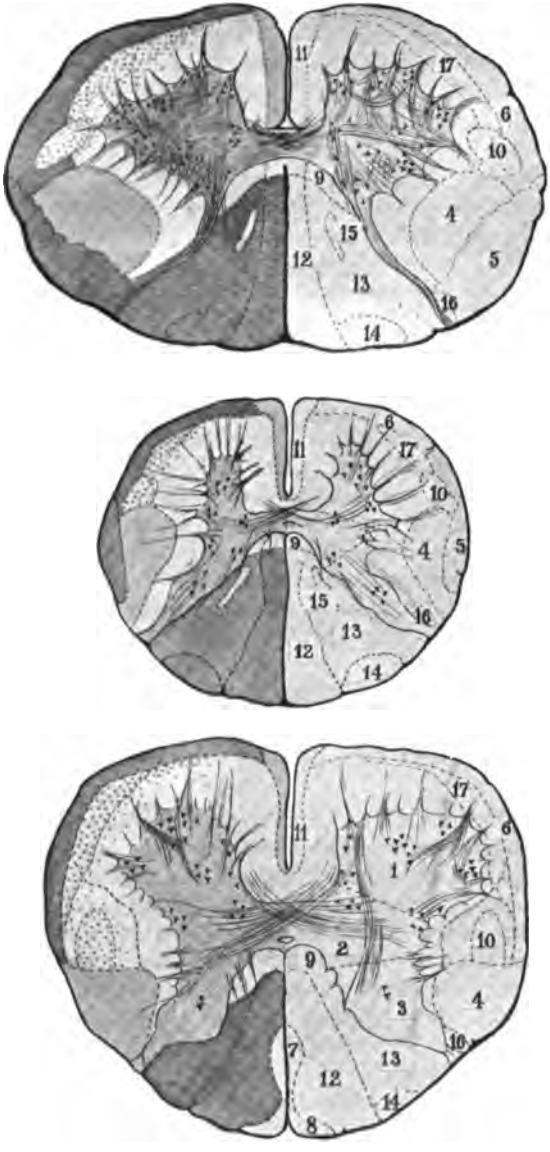


FIG. 7.—DIAGRAM TO SHOW THE VARIOUS ENDOGENOUS AND EXOGENOUS TRACTS OF THE SPINAL CORD.

1, Anterior horn ; 2, commissural fibres ; 3, posterior horn; 4, crossed pyramidal tracts ; 5, direct cerebellar tract ; 6, antero-lateral (Gower's) tract ; 7, oval area of Flechsig (endogenous) ; 8, Gombault and Philippe's tract (endogenous) ; 9, cornu commissural tract (endogenous) ; 10, the rubro-spinal and spino-thalamic tract ; 11, direct pyramidal tract ; 12, the postero-median column of Goll ; 13, the postero-external column of Burdach ; 14, postero-internal triangle (endogenous) ; 15, comma tract (endogenous) ; 16, Lissauer's tract ; 17, tecto-spinal, spino-tectal, vestibulo-spinal, and cerebello-spinal fibres.

and vestibulo-spinal tracts. Degeneration in both antero-lateral columns will be more marked in cases of transection of the cord than will occur from a degeneration of the pyramidal fibres from a lesion of the motor area of the cortex or from destruction of the pyramidal fibres as they pass through the internal capsule.

**Degeneration of the Proprio-Spinal Fibres.**—The term "proprio-spinal" has been given by Sherrington to a mass of fibres surrounding the grey matter of the spinal cord, and which belong purely to the spinal cord. They consist of both ascending and descending fibres, and they connect up the nuclei of the spinal segments with the cranial nerve nuclei, and integrate the reflex arcs. They vary in length, but all the segments are connected by means of these fibres, so that some extend the whole length of the cord. In a transverse lesion of the cord a number of these fibres will consequently be found to be degenerated both above and below the lesion. Lesions such as a myelitis, involving any extent of grey matter, will cause considerable degeneration of these fibres, as well as destruction of the spinal motor neurones and the sensory terminals in the grey matter.

## Cerebral Localization.

In the brain differentiation of function is most highly developed, and morbid processes are not infrequently so localized as to lead to the derangement of some particular function. Accordingly, it becomes necessary to give a brief account of the functions of the brain in so far as localization of disease is concerned. To and from various areas of the cerebral cortex of each hemisphere long axis cylinder processes, arising from large cells, pass through the corona radiata, internal capsule, and corpus callosum, and connect the cerebral hemisphere with other portions of the nervous system. These proceed to, and come from, the opposite cerebral hemisphere, basal ganglia, mesencephalon, pons Varolii, medulla, and each segment of the spinal cord. These so-called "extrinsic" fibres are known as the "cortical projection system." The main mass of the brain is composed of shorter axis cylinder processes arising from smaller cells which bring the different parts of the cortex into association one with another: thence they are known as the "association system." There are four main areas of the cortex whose cells would seem to furnish only fibres of the association system—namely, the prefrontal lobe, main portion of the temporal lobe (excepting the uncinate gyrus and the superior temporal convolution), the inferior parietal lobule, and the external surface of the occipital lobe. These areas were described by Flechsig, who applied to them the term "sensory annexes." As an example, the posterior portion of the superior temporal convolution may be cited as an annexe to the hearing centres.

The destruction of this area on the left side of the brain in right-handed people leads, not to loss of hearing, but of the more essential psychical function dependent on the sense of hearing, since loss of the power of understanding spoken words (word-deafness) results. It is probable that these four areas, so closely connected together by association tracts, are closely connected with the higher psychical processes, and that they are of equal value, since extensive lesions in any of these regions may produce considerable mental impairment. The indication would seem to be, therefore, that, contrary to the opinion of many, prefrontal convolutions are of little more importance than the other areas mentioned.

Various monoplegias in man have been noted as the result of localized vascular lesions, and the Rolandic area has been mapped

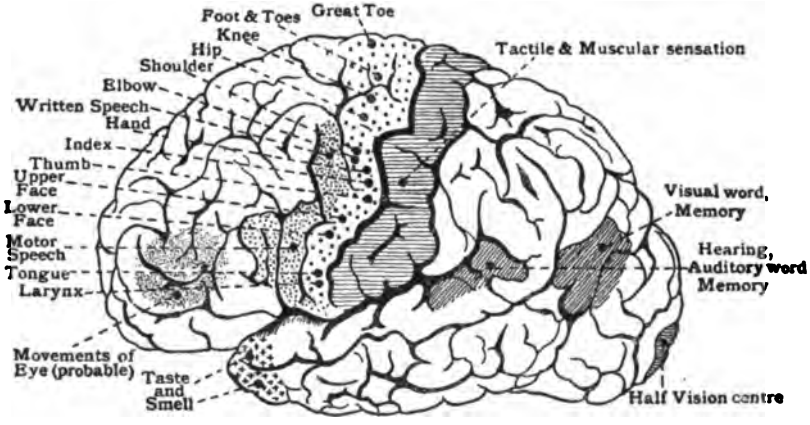


FIG. 8.—LEFT HEMISPHERE, SHOWING THE SITUATION OF THE HUMAN CORTICAL PROJECTION CENTRES. (MODIFIED AFTER SHERRINGTON AND GRÜNBAUM.)

out into definite regions corresponding with those determined by stimulation in the monkey by Horsley, Sherrington, and others. As a result of a recent piece of work by Gordon Holmes and Page May, in which the spinal cord was divided in monkeys at various levels, and the brains examined for degeneration at subsequent periods, it was found that the degeneration and total disappearance of Betz cells corresponded exactly with the stimulation area. Those areas concerned with motor phenomena, the Betz cells of which give rise to the pyramidal tracts, are entirely situated in the pre-Rolandic portion of the central convolution. Local destruction of the pre-Rolandic central convolutions gives rise to paralysis of voluntary movement of the opposite side. If a movement, however, involves muscles of both sides of the body, the whole movement is weakened, but not abolished, by a unilateral lesion.

Examples are seen frequently in hemiplegia where the movements of the lips, larynx, and trunk, are not paralyzed. Lesions of the post-Rolandic central convolutions do not usually produce any gross sensory disturbance, notwithstanding the fact that this area receives a great many sensory fibres from the thalamus. Certain defects are, however, usually present, consisting in delayed tactile appreciation and want of localization of touch, especially in the peripheral portions of the limbs. The fact that there is only slight loss of sensation is probably due to branching and wide distribution of the sensory fibres in the cortex. Want of localization would be expected where some of the end-stations of branching tactile fibres are destroyed, since all of these end-stations must be intact, and must be brought into communication one with another by association neurones for localization to be perfect. Fibres conveying muscle and joint sense impressions mostly terminate in this region; hence destructive lesions are usually accompanied by considerable impairment in the sense of position in limbs of the opposite side. As a result of a combination of impairment of localizing power of tactile impressions and impaired sense of position, together with the destruction of association fibres from the occipital region, astereognosis, or loss of the power to recognize shape and form of an object, sometimes occurs.

Irritative lesions of the pre-Rolandic cortex, not causing destruction of the Betz cells, produce localized Jacksonian fits in structures of the opposite side of the body corresponding to motor representation in the area of cortex involved. The common morbid conditions causing Jacksonian epilepsy are—(*a*) Localized meningitis, (*b*) tumours, (*c*) trauma with scar tissue. More often than not the lesion is not in the motor area, but either in front or behind, when Jacksonian epilepsy occurs without monoplegia. Irritative lesions of the post-Rolandic central convolutions may be at times accompanied by sensory Jacksonian fits consisting in various paræsthesiæ affecting part or the whole of the opposite side of the body, according to the extent of cortex irritated.

**Frontal Lobe.**—This lobe receives its blood-supply from two sources—the anterior cerebral artery and the middle cerebral artery. The former supplies the whole of the medial aspect and the greater portion of the orbital surface, the remainder being supplied by the branches of the middle cerebral. A large projection system of fibres connects the frontal lobe with the opposite side of the cerebellum through its connections with the pontine nuclei. Hence in extensive lesions of the frontal lobe disturbances of equilibration are not infrequently met with, simulating those with cerebellar disease. The anterior two-thirds of the frontal lobe would seem to be concerned with psychical functions. In the posterior third of the left frontal lobe, immediately in front of the precentral gyri, are situated centres of the highest importance, where

motor complexes are largely co-ordinated, and from which they are initiated by impulses passing from this region to the true motor cortex. Broca's area is the best known of these centres, and here is situated a centre for the co-ordination of movements of the musculature used in speech. Movements of the larynx, tongue, etc., are here combined previous to the innervation of the musculature itself by means of impulses from the lower portion of the pre-Rolandic cortex. Destruction of Broca's area does not produce any paralysis of the muscles concerned in the production of speech, but rather the delicate co-ordination of their action, which is necessary for speech, can no longer be initiated. Hence the patient suffers from motor aphasia. Similarly, there is every reason to believe that in the posterior portions of the first and second frontal convolutions like centres are situated where movement complexes are initiated for the limbs, the movements being here largely combined before the innervation of the motor cortex. Since these centres are unilateral, it is necessary that the corpus callosum should be intact in order that no signs of apraxia be present. From the above brief discussion it will be observed that motor aphasia and agraphia are really forms of apraxia, the former of the speech musculature, and the latter of the hand-and-arm musculature used in writing. A patient suffering from motor apraxia understands perfectly any command given to him, such as the turning of a key in a door; knows perfectly well what he ought to do, but is unable to execute correct co-ordinated movements, although there is no actual paralysis present. In human beings the centre for movement of the head and eyes is situated well forward, as shown in the diagram. Extensive destructive lesions of the frontal lobe situated in the prefrontal region may be associated with practically no symptoms, but there may be every degree of mental impairment—slight irresponsibility, loss of memory, hebetude, and not infrequently, when there is extensive destruction, incontinence of urine and fæces occurs. Definite localizing signs, however, occur when the centres above-named are either irritated or destroyed.

The **Occipital Lobe** receives its blood-supply from the posterior cerebral artery. The projection system consists of fibres of the optic radiation prolonged from the optic tracts, and terminating in the striate area of the occipital cortex, which is situated within the calcarine fissure and along the margin of the gyri which bound it. This striate area is delimited by the presence of the line of Gennari, which may be distinctly seen on cross-section of the cortex in this region. In highly developed brains the striate area is practically confined to the mesial surface of the occipital lobe, owing to the great development of the parietal lobule and the visuo-psychic (associational) portion of the occipital lobe, the striate area thus being pushed backwards. In lower types of brains, however, it

extends to a variable degree on to the external surface of the lobe. This area constitutes the half-vision centre; the upper margin of the calcarine fissure corresponds to the upper half of the retina, while the lower half represents the remainder. The macular region, however, is probably bilaterally represented. The lobes of the two hemispheres have a well-marked connection through the splenium of the corpus callosum, and many fibres of the line of Gennari are derived from this source. Destructive lesions of the occipital lobe are frequently associated with homonymous hemianopia when the striate area is involved. Such homonymous hemianopia may be quadrantic if the lesion involves only the upper or lower half of the striate area. Owing probably to its bilateral representation, or, as Monokow suggests, to its representation in this angular gyrus, the macular region is usually intact in unilateral lesions. Sensory epilepsy, consisting of visual hallucinations, is occasionally met with in conditions leading to irritation of the occipital cortex.

**Temporal Lobe.**—The vascular supply is from two sources, the middle cerebral and the posterior cerebral arteries, the former supplying the first and second temporal convolutions on the convex surface, while the latter supplies the inferior and mesial surfaces. By the temporo-pontine fibres the temporal lobe is indirectly connected with the cerebellum of the opposite side, so that widespread lesions in this lobe are not infrequently associated with some disorders of equilibration. One set of corticipital fibres connects the temporal lobe with the optic thalamus, while another set passes to it from the inferior colliculus ending in the first temporal gyrus. Each olfactory tract is continued into the uncinate gyrus of either side, in which also fibres conveying taste impressions terminate. Destructive lesions situated in the anterior portion of the temporal lobe may show no signs, except perhaps some slight mental impairment, such as occurs in lesions of the prefrontal and occipital lobes. Unilateral lesions of the temporal lobe are not accompanied by any marked impairment in acuity of hearing, taste, or smell, since the representation of all these senses is bilateral. Bilateral lesions involving the posterior third of the first temporal and the transverse gyri of Heschl within the Sylvian fissure produce cortical deafness. Unilateral lesion of the left hemisphere causes a temporary loss of word memory pictures in the initiation of speech, there is always a considerable degree of paraphasia, and if the subcortical association tracts, connecting this region with the angular gyrus and Broca's convolution, are largely involved, the patient is unable to understand the meaning of written language, although he may be able to copy the symbols, and the whole function of ideation is considerably interfered with. Slight lesions of these convolutions on the left side produce minor degrees of word-deafness, paraphasia, paragraphia, and ideational apraxia. Irritative lesions in the

region of the uncinate gyrus may be associated with olfactory and gustatory hallucinations.

**Inferior Parietal Lobe.**—This area comprises mainly the supramarginal and angular gyri, and receives its vascular supply mainly from the posterior branches of the middle cerebral, but to a certain extent from branches of the posterior cerebral. It receives a great many afferent connections from the optic thalamus, and has a large connection with its fellow of the opposite side through the corpus callosum. Destructive lesions of the left angular gyrus are associated with varying degrees of word-blindness, but the power of recognizing objects, and even of reproducing them on paper, is not infrequently practically undisturbed. In subcortical lesions which involve the association fibres connecting this area with the temporal lobe and Broca's area, the mechanism of speech is to some extent interfered with, and varying degrees of paraphasia are exhibited.

It must not be forgotten that such an attempt to isolate the brain in separate physiological areas is highly artificial, and that the brain functionates as a *whole*, the right side acting in unison with the left, and probably by way of the corpus callosum supplying largely the afferent energy, which it has received from the periphery, for processes which take place more essentially in the left hemisphere.

## Inflammation of the Meninges.

Three membranes enclose the central nervous system, but owing to the intimate connections of the pia mater and arachnoid these two always suffer together, and for practical purposes may be considered as one. Inflammation of the dura mater is termed "pachymeningitis," while inflammation of the pia arachnoid is usually termed "leptomeningitis." These conditions are necessarily frequently associated, but nevertheless a distinction must be made, since in many cases the one suffers primarily, and the affection of the other is secondary.

**Pachymeningitis.**—The dura mater consists of two layers; the outer forms the periosteum for the cranial bones, following exactly the internal cranial surface, and becoming continuous with the external periosteum at the edges of the various cranial foramina. The spinal dura mater is not actually continuous with the cranial membrane, the two structures being attached separately to the edges of the foramen magnum. The inner layer of the dura mater forms the projecting processes—falx cerebri, falx cerebelli, and the tentorium—and is covered with a delicate, smooth, endothelial surface. Pachymeningitis is in the majority of cases the result of some morbid inflammatory process in the subjacent bone, and may be looked upon as really an internal periostitis analogous to that periostitis occurring as the result of injury to, or disease of, other

bones. It may arise as the result of infective processes occurring in the nasal cavity, the pharynx, the orbit, or the middle ear, and is frequently suppurative. The dura mater is at first œdematous and congested; later it may be covered with pus, which separates it from the bone and infiltrates its substance, so that occasionally a collection of pus may occur between the dura mater and the bone. Such collections, if of a chronic nature and of any considerable size, may give rise to symptoms, owing to the pressure which they exercise, and thus simulate chronic abscess of the brain or cerebral tumour. More rarely this condition may be secondary to disease of the bones of the skull, due to syphilis or wounds, but such cases are now seldom seen, owing to the improvement in asepsis and antisepsis. Pachymeningitis affecting the spinal dura mater is most frequently tubercular in origin, and occurs in association with spinal caries, in which case there is not infrequently an accumulation of tubercular granulations and caseating débris outside the dura mater. Such collections of tubercular material not infrequently lead to a condition of paraplegia, partly owing to the compression of the spinal cord produced by them, and partly owing to the obliteration of bloodvessels which enter each nerve root, thus cutting off, or at least interfering with, the blood-supply to the cord. Syphilitic pachymeningitis of a gummatous nature, and unassociated with obvious bone disease, which gives rise mainly to symptoms of nerve-root involvement, is not infrequently met with.

**Internal Pachymeningitis** is characterized by the formation of a false membrane, usually very vascular and consisting of several layers. Owing to the rupture of small bloodvessels, blood-cysts are often found between the layers, and are called *hæmatomata* of the dura mater. The false membrane which usually brings about the adherence of the dura mater to the pia arachnoid may extend over the greater part of one or both hemispheres. This condition is met with most frequently in cases of general paralysis and chronic alcoholism.

**Leptomeningitis.**—The pia arachnoid resembles in many respects the serous membranes of the body cavities; the pia mater follows exactly the external surface of the brain, dipping into the sulci, and projecting into the ventricles along the transverse fissure, where it carries the choroid plexus on its free edge and under-surface into the third and lateral ventricles. The whole pia is extremely vascular, and from its internal surface great numbers of tiny blood-vessels penetrate the brain substance at right angles to its surface. Hence any extensive inflammation of the pia mater must necessarily give rise to grave interference with the cerebral circulation, and the actual tissue continuity between the brain substance and the pia mater necessarily means that in any inflammation of the latter the superficial portions of the former must be involved—*i.e.*, in all cases of leptomeningitis there is associated encephalitis.

It must be remembered that the arachnoid space of the brain is continuous with that of the spinal cord and with the cavities of the whole ventricular system, so that if infection takes place it is not difficult for such infection to become extremely widespread.

Inflammation of the pia arachnoid is mainly, and perhaps in all cases, due to the growth of micro-organisms which have gained access to the arachnoid space. The most important form is tubercular, the primary lesion often being a tonsil infected with bovine tubercle by milk. A number of other causes of infection exist, which may be considered under the headings *local* and *general*.

LOCAL.—1. Traumatic injuries of the head with direct infection.

2. Adjacent disease outside the dura mater—suppurative otitis, chronic ear disease with caries of the mastoid or petrous portions of the temporal bone, and occasionally disease of the bones of the nose or orbit. The infection in these cases may spread directly, or along the course of lymphatics or bloodvessels. It is probable that some cases of meningitis in which no visible organic cause is found post mortem may have arisen by the infection gaining access to the middle ear by the Eustachian tubes.

3. Tumours and abscesses of the brain may cause inflammation of the adjacent meninges.

GENERAL.—Meningitis may occur in the course of certain infective diseases—*e.g.*, smallpox, scarlet fever, measles, septicæmia, gonorrhœa, pneumonia, and acute rheumatism. Cerebro-spinal meningitis, due to a specific diplococcus, may also occur in an *epidemic form*. A form of meningitis described by Barlow and Gee, designated *posterior basic meningitis*, is also due to the same diplococcus. It affects infants and young children, and one-half the cases are fatal. Meningitis in rare instances has followed a blow not causing any wound, and it has been found post mortem in some cases of sunstroke. Thickening and opacity of the membranes also occur in chronic wasting degenerative processes of the central nervous system—for example, general paralysis, and occasionally chronic alcoholism with dementia. The process is here generally considered to be *secondary* to the atrophy.

**Morbid Anatomy.**—When the infection is local, the meningitis may be circumscribed; but when the cause is some infective blood-condition, it is usually generalized, and may in some cases affect the spinal as well as the cerebral meninges—*e.g.*, meningitis occurring in the course of pneumonia may in many ways resemble the epidemic form. Tubercular and syphilitic meningitis usually affect the *base* primarily and especially, whereas in other forms the *convexities* of the hemispheres are affected. Certain changes are common to all forms of meningitis. The pia mater is intensely hyperæmic and red, as if the vessels had been artificially injected. Soon opacity and thickening of the membranes occur, recognizable

most readily in the arachnoid, and along the course of the vessels there is an opacity owing to distension of the perivascular lymphatic sheaths. An inflammatory exudation from the bloodvessels of the pia mater occurs; this may be serous, sero-purulent, or purulent, and is manifest especially in the sulci of the convexity and in the spaces at the base of the brain. In severe cases pus mixed with fibrin forms a continuous opaque yellowish layer under the visceral layer of the arachnoid. The inflammation usually spreads to the adjacent structures, causing neuritis, myelitis, encephalitis, and, later on, adhesions. The ventricles of the brain and the interpeduncular subarachnoid space may be distended with a turbid serous fluid, and the choroid plexus and the velum interpositum are usually congested and swollen. This fluid, examined microscopically, may be found to contain micro-organisms, leucocytes or pus cells, and large granular epithelial cells.

The suppurative process is extremely marked, and often very rapid in formation, in epidemic cerebrospinal meningitis.

**Effects.**—The first stage, or *period of excitation*, is characterized by *headache, delirium, rigidity*, and *general* or *local convulsions;* these symptoms can be accounted for by the irritation, in early stages of inflammation, of the cortex, crus, pons, and medulla, or of the spinal cord and nerves. The second stage, or *period of depression*, occurs as the inflammation extends into the cortex, and *paralyses* of various kinds occur as the result of affection of the motor nerves; the sixth nerve, owing to its long course, is especially liable to be affected, giving rise to internal strabismus and diplopia. In the final stage the increasing effusion into the skull causes a rise of intracranial pressure, and this, together with the encephalitis which is necessarily associated with the meningitis, induces *coma.*

### Cerebrospinal Fluid.

It is convenient here to consider briefly the nature of the changes which occur in the cerebrospinal fluid as the result of disease.

The cerebrospinal fluid is almost entirely the result of secretory activity of the choroid plexus. There is every reason to believe that a quantity of cerebrospinal fluid is continually being secreted, and that it fills up all spaces, cracks, and crevices, in the subarachnoid space and its annexes, a quantity proportional to the amount secreted continually escaping under conditions of health, partly by the venous sinuses, as shown by Cushing, and partly by means of communications with the lymphatic system at the place of exit of the spinal and cranial nerve roots. The pressure on the whole cerebrospinal axis is thus uniformly maintained, but where the vessels of the pia arachnoid run in the sulci or dip into the substance of the brain the layer of the arachnoid follows like a sleeve, forming

thus a canalicular system in the nervous substance, and containing cerebrospinal fluid. This canalicular system surrounds the perivascular lymphatics where they exist. The uniform pressure of the fluid sleeve which surrounds and supports the bloodvessels of the nervous system is of great importance in determining largely the amount of vascular flow, since the vessel walls are relatively thin and vasomotor control unimportant. Any marked alterations of pressure brought about by increase or decrease of cerebrospinal fluid thus exercise effects of serious import on the vascular supply. The whole central nervous system being contained in a closed space, the cerebrospinal fluid fills up all the space which is not occupied by tissues or blood, serves to equalize the pressure throughout, and acts as a water-cushion, especially at the base of the brain. These functions of the cerebrospinal fluid can only be properly subserved if the rates of secretion and outflow of the cerebrospinal fluid are proportional, and these presuppose also the absence of any blockage either in the egress of fluid through the iter or through the foramen of Magendie. A case reported in the *Archives of Neurology* illustrates the effect of intermittent blockage of the iter by a small tumour growing from the choroid plexus. The intermittent internal hydrocephalus with associated cortical anæmia produced sudden transitory attacks of drowsy lethargy, deepening occasionally to complete coma, with varying epileptiform convulsions.*

From the experiments of Mott and Hill on cerebral anæmia, produced by ligation of both carotids and one vertebral artery in the monkey, it is probable that the cerebrospinal fluid acts as a special lymph of the brain and constitutes the ambient medium of the neurone. The brain is the last organ to suffer in starvation, and we may presume that its metabolism, although extremely complex, is slight. It is possible that the fluid acts as the medium of exchange between the blood and the cerebral tissues. The experiments of Verworn are of interest in this relation (*vide* p. 338), and it is evident that the organic material and the oxygen supplied by the fluid are essential for nervous activity. We may also suppose that the products of activity are continually being neutralized and removed by the slightly alkaline fluid. Cavazzani has shown that the alkalinity of the cerebrospinal fluid is least after functional activity. The researches of Mott on the gaseous content of the fluid have shown that it contains a high carbon dioxide value and tension, and that the gas, as a result of metabolic processes, is capable of absorption in the fluid until it is finally carried away in the blood-stream.

**Examination of Cerebrospinal Fluid.**—The fluid is obtained by the simple operation of lumbar puncture somewhere below the second lumbar vertebra, in order that all chance of injury to the

* *Archives of Neurology*, vol. i.

spinal cord may be avoided. Normal cerebrospinal fluid is colourless and quite clear, with a specific gravity of 1006 to 1008. It contains the faintest trace of sero-globulin and of albumose, and of a copper-reducing substance which gives glucosazone crystals. It is distinctly alkaline. Microscopically, a few flat endothelial cells and an occasional lymphocyte may be observed.

**Morbid Conditions of the Cerebrospinal Fluid.**—Instead of being clear like water, the fluid may be opalescent, turbid, or even purulent, as in some cases of acute meningitis. In rare cases of extreme jaundice the fluid has been observed to be bile-stained, but this is the exception; for in most cases of jaundice the cerebrospinal fluid is unstained, but where inflammation upsets the secretory mechanism there bile may appear. Blood-stained cerebrospinal fluid is not infrequently found in cases of cerebral or spinal hæmorrhage, while some days after such a hæmorrhage the fluid may be distinctly yellowish in appearance.

Certain observations have been made showing that the composition of the cerebrospinal fluid becomes altered in disease; for example, in uræmia, urea, ammonia, and other products of nitrogenous metabolism, may be found in appreciable quantities; in diabetes the sugar is increased, and diminishes *pari passu* with the diminution of sugar in the blood and urine as a result of dietetic treatment. Sugar is diminished or absent in most cases of extensive meningitis. A marked excess of albumin is present in all cases of acute meningitis, and to a lesser extent in general paralysis; while in cases of tabes, unless the disease be in a very active stage, there is no marked excess of protein constituents. In degenerative conditions of the central nervous system cholesterol can be detected in the cerebrospinal fluid, the quantity apparently being in proportion to the degree of wasting.

Recent research concerning syphilitic and parasyphilitic diseases of the nervous system points to the great importance of testing the cerebrospinal fluid for Wassermann's reaction, especially in suspected cases of general paralysis. The test may be carried out in the following manner: It is necessary first to immunize an animal against the blood of some other animal; for example, the blood-corpuscles of an ox are injected into the circulation of a rabbit. After several injections the blood-serum of the rabbit becomes hæmolytic to the blood-corpuscles of the ox by virtue of the presence in the serum of an immune body plus the normal complement, or cytase. The latter is removed from the rabbit's serum by heating to 56° C. for thirty minutes. There is then left in the rabbit's serum the immune body, which by itself will not dissolve the red blood-corpuscles of the ox. The addition, however, of a small amount of guinea-pig's serum which contains complement will at once restore its hæmolytic properties. The actual experiment consists in mixing the serum or cerebrospinal fluid to be examined

in varying dilutions with a watery or alcoholic solution of the liver of a syphilitic fœtus ; a small amount of the serum of a guinea-pig is added, and the bulk made up to a constant volume (about 2 c.c.) with saline solution. The series of tubes containing these mixed solutions are placed in an incubator at 37° C. for one hour, and then the "sensitized corpuscles" are added (by "sensitized corpuscles" is meant washed blood-corpuscles of the ox to which has been added the heated rabbit's serum). The mixtures are again placed in an incubator for two hours at 37° C., then removed and placed on ice overnight. The next morning the amount of hæmolysis in each tube can be estimated. If, on the one hand, antigen (contained in the extract of the syphilitic liver) and antibody (in the serum or cerebrospinal fluid) have been present, they have united with the complement (provided by the serum of the guinea-pig), and no solution of the corpuscles will have taken place, because the complement has been fixed before the addition of the sensitized corpuscles.

If, on the other hand, the immune body (antibody) was not present in the serum or cerebrospinal fluid, then the complement in the guinea-pig serum has remained free to act on the sensitized corpuscles, and lead to their solution (hæmolysis). A control experiment using normal serum or cerebrospinal fluid—viz., one which contains no antibody—must be made at the same time.

The simpler method of Noguchi consists in boiling 2 parts of cerebrospinal fluid with 5 parts of a 10 per cent. solution of butyric acid in saline solution for a few seconds, and then adding 1 part of a normal sodium hydrate solution and again boiling briefly. A flocculent or granular precipitate is obtained in parasyphilitic affections, due to the presence of a globulin. It is useful in distinguishing general paralysis from other forms of insanity not associated with meningo-encephalitis. The fluid must be free from blood.

The Nonne-Apelt test for the presence of globulin consists in mixing together equal quantities of a saturated solution of ammonium sulphate and the cerebrospinal fluid, when a cloud arising within three minutes denotes a positive reaction. The Ross-Jones modification of this test allows the fluid to gently flow on to the surface of saturated ammonium sulphate solution, and the formation of a clear-cut, greyish-white ring at the junction of the two liquids constitutes a positive reaction.

The exact nature of the substances concerned in the Wassermann reaction is still quite unknown, but it has been shown that the antigen obtained from the syphilitic liver may be replaced in the reaction by lecithin, soaps, and other lipoids; while the immune body of the cerebrospinal fluid present in general paralysis and in active tabes cannot be separated from the globulins, and is probably in itself of globulin nature. The importance of this test in the diagnosis of parasyphilitic affections, and especially in general paralysis, cannot

be over-estimated. Ninety-seven per cent. of the cases of general paralysis examined at Claybury by Candler and Henderson Smith gave a positive result, while in all cases of insanity other than general paralysis the result obtained was uniformly negative.

In contradistinction to the results obtained in tabes and general paralysis, negative results have usually been obtained in cases of syphilitic disease of the cerebrospinal axis.

**Cytological Examination.**—In order to examine the cerebrospinal fluid microscopically, it is in most cases necessary to carefully centrifuge the specimen for about five minutes. After decanting off the supernatant fluid, the residue is taken up with a capillary pipette, blown out on to a slide, allowed to dry, and then stained with Leishmann's or Jenner's stain. At the same time it is well to determine the number of cells per cubic millimetre by placing a drop of the original fluid in a Fuchs-Rosenthal counting chamber. The most important thing to be determined is the presence or otherwise of leucocytes; not only the numbers, but also the kinds of leucocytes, must be observed. In cases of acute microbic infection of the brain and meninges, especially the suppurative varieties, a leucocytosis is present, and there is a great excess of the polymorphonuclear leucocytes, with occasional large mononuclear types to be seen. During recovery from an acute attack, the polymorphonuclear variety becomes gradually replaced by lymphocytes, which may be present in excess for some time. Cases of cerebral abscess, where there is no involvement of the neighbouring meninges, may show no cytological alteration in the cerebrospinal fluid. In subacute and chronic infections of the meninges, whether tubercular, syphilitic, or otherwise, and in such conditions as tabes and general paralysis, there is a marked excess of lymphocytes, usually accompanied by simultaneous excess of large mononuclears and plasma cells. Not infrequently in cases of herpes zoster, lymphocytosis may also be observed. In cases where tubercular meningitis is of an acute and fulminating character, there may be a large excess of polymorphonuclear leucocytes, together with the lymphocytes; hence the appearance of the polymorphonuclear variety in the cerebrospinal fluid would seem to depend, not so much on the nature of the infection, but rather upon its acuteness and severity. In cases of apical pneumonia simulating cerebrospinal meningitis, the absence of any changes in the cerebrospinal fluid obtained by lumbar puncture will often be of very great help in determining the correct diagnosis.

Alzheimer's method for differential cell examination consists in adding alcohol to the cerebrospinal fluid, imbedding in celloidin the precipitate obtained on centrifuging, and cutting and staining serial sections.

**Bacteriological Characters.**—Bacteriological examination is chiefly of value in cases of meningitis. For immediate examination the

same method may be used as that described for cell examination, but it is wise in doubtful cases to make cultures on various media, and to carry out inoculation experiments on guinea-pigs. In epidemics of cerebrospinal meningitis and in cases of posterior basic meningitis, microscopic examination of the fluid usually is sufficient to show the Gram-negative-staining diplococcus of Weichselbaum. Other organisms occasionally found as causal agents in acute meningitis are the staphylococcus, streptococcus, gonococcus. In cases of tubercular meningitis it is often very difficult to discover tubercle bacilli unless by an inoculation experiment. It is better not to centrifuge the cerebrospinal fluid when searching for tubercle bacilli, but rather to allow the fluid to stand overnight, and then to examine the fine coagulum that forms for the bacilli. If this method is adopted, a positive result is often obtained in cases in which the centrifuge deposit is negative. In cases of sleeping sickness, the *Trypanosoma Gambiense* may be present in such large numbers as to be found without centrifuging, and in practically all cases careful search discloses its presence in the cerebrospinal fluid.

### Encephalitis.

Besides the cases of encephalitis occurring as a complication of meningitis and as the result of infection after traumatism, there remain two important groups to be discussed: (1) Encephalitis occurring during the course of, or immediately following, some acute infectious disease; (2) a large group of cases occurring as the result of a probably specific infection.

By far the greater number of cases occurring during infectious diseases are associated with measles, scarlet fever, and pertussis, while occasional cases occur during the course of most other infectious diseases. From the nature of the causal agent in these cases, it will readily be understood that the vast majority of cases of encephalitis occur in infancy or early childhood. In the second group of cases referred to, the disease also occurs in infancy or early childhood. It frequently attacks a child previously, and up to the time of onset, in good health. The onset is acute; the disease is usually ushered in by convulsions and febrile temperature, and more or less coma supervenes. The associated paralysis is usually mono- or hemiplegic in type, but may occasionally be diplegic. It has been suggested that these cases are the result of the same specific infection which is the causal agent in cases of anterior poliomyelitis. Nevertheless it is extremely rare to find the two conditions associated in the same individual. On the other hand, cases have been reported where in the same family and at the same time one child has suffered from anterior poliomyelitis, while another has suffered from encephalitis. It is impossible to say definitely what is the relationship, if any, between the two conditions, since in neither

case has the specific organism yet been isolated. Post-mortem appearances of the brain in encephalitis are very characteristic. The area or areas involved are swollen, purplish-red in appearance, with the edges gradually fading into the surrounding tissue. Small subpial hæmorrhages are frequent, and the pia itself is somewhat engorged; but for the most part the overlying membranes are strikingly free from involvement in the inflammatory process. A section of the brain shows that the lesion does not extend for any distance into the white matter. Microscopically the appearances are typical of those of other acute inflammatory conditions. Such a condition may either completely resolve or may lead to a varying degree of local destruction, with subsequent cicatrization.

In some cases the cerebellar cortex is the main seat of the inflammatory process, and the diagnosis of the condition in its early stages is often extremely difficult, owing to the marked similarity of the symptoms to those seen early in acute meningitis. An examination of the cerebrospinal fluid is here of great use, since in cases of cerebellitis it is either normal or contains only a slight excess of lymphocytes and protein content. Later, when the marked general symptoms begin to subside, the characteristic ataxia and titubation, which become more pronounced if the child is raised from the reclining position, render the diagnosis certain. Owing to the homogeneity of the cerebellar cortex, and the fact that it is simply an afferent relay station, compensation readily takes place, and, unless the cortical destruction be very widespread, the ataxic manifestations usually clear up entirely after some time.

**Cerebral Abscess.**—The causes of this condition may be divided into local and distant. By far the most frequent *local* cause of cerebral abscess is *chronic ear disease.* Inflammation of the middle ear or mastoid cells is often followed by a purulent discharge and by *caries of the bone.* Not infrequently arrest of the discharge is followed by abscess. Occasionally there may be no bone disease, only suppurative inflammation of the middle ear or mastoid cells; and in such cases the infection probably passes by the perivascular lymphatics along the veins which connect the tympanic cavity and mastoid cells respectively with the superior petrosal and lateral sinuses. Disease of the nose and orbit, syphilitic caries of other bones, tumour of the brain, and injury, are among the rarer causes of cerebral abscess. *Distant causes* are pyæmia, gangrene of the lung, fœtid bronchitis, bronchiectasis, and empyema—all rarely met with.

**Morbid Anatomy.**—Abscesses are usually solitary, but there may be several, and in pyæmia sometimes many. In size they are rarely less than that of a walnut, and may even involve the greater part of a cerebral hemisphere. Owing to the frequency with which ear disease acts as a cause, abscess is met with most often in the temporo-sphenoidal lobe and the lateral lobe of the cerebellum. In

nasal and orbital disease it is usually found in the adjacent frontal lobes. In chronic cases the abscess cavity is limited by a well-defined capsule. The more acute the abscess, the less tendency is there for it to be circumscribed.

The process of *suppuration* commences with inflammatory softening, cell infiltration replacing and destroying the normal structure. Pus is formed which, in the case of ear disease, is usually of a greenish colour, and frequently of fœtid odour and acid reaction. It is made up of pus corpuscles, degenerated cells, fat, cholesterin, hæmatoidin, and micro-organisms, usually staphylococci and streptococci. The pus is contained at first in an irregular cavity, and there is a tendency for the abscess to increase by necrosis of portions of the limiting tissue. It may thus, by spreading, burst into the lateral ventricles or externally. It may, however, become encapsuled by connective tissue; the pus, undergoing mucoid degeneration, then becomes thick and viscid. It is thought that pus thus encapsuled may dry up and caseate or calcify, or even be completely absorbed, leaving little more than a scar. The symptoms produced by abscess depend upon local irritative effects of the infective inflammation, septic absorption, and, in severe cases, intracranial pressure.

## Inflammation of the Spinal Cord.

**Myelitis.**—The term "myelitis" should be applied only to conditions of true inflammation of the spinal cord, but it has, unfortunately, been used at one time or another for all forms of degeneration of the spinal cord, whether of true inflammatory origin or otherwise. Even to-day, perhaps, the most common application of the term is to cases of so-called "compression myelitis," due to compression of the spinal cord by tumours, cysts, bony malformations, tuberculous and syphilitic infiltration of the membranes, and extradural collections of caseous material in tubercular caries. In such cases examination of the spinal cord post mortem reveals signs of true inflammation, but the degenerations present are partly the result of anæmia, and perhaps vascular obliteration with surrounding œdema, brought about by the localized pressure. Another group of cases usually included by the term "myelitis" embraces conditions of syphilitic gummatous infiltration of the cord, and, more rarely, tuberculous infiltration. In such cases it is wise to look upon these conditions simply as a localized manifestation of the systemic disease present, since the microscopical findings are not those of true acute inflammation, but are the same as those to be found in syphilitic or tubercular foci in other parts of the body. Excluding these conditions, there are still a considerable number of cases which occur without any marked implication of the meninges or other surrounding tissues, and where there is a diffuse inflammation usually somewhat localized

in vertical extent, and involving more or less all the tracts, irrespective of their nature or origin. Such a condition may be acute or subacute in its onset, and when limited to the grey matter is termed *poliomyelitis*. Even in these cases there may be considerable variations in the amount of inflammatory reaction present, and in cases due to acute toxic action, with rapid localized degeneration of the neural elements, and where possibly no actual micro-organisms are present, there may be practically no leucocytic infiltration of the cord and comparatively slight vascular engorgement. In other cases, however, all the signs of acute inflammation may be manifest, with vascular dilatation, extravasation of red cells, and leucocytic emigration, and where resolution does not occur, thrombosis of small vessels and actual pus formation may be found.

Cases of softening of the spinal cord secondary to vascular occlusion of non-infective origin must be similarly excluded when discussing conditions of true myelitis.

**Etiology.**—In many cases we are still bound to acknowledge our inability to ascertain the cause of the inflammation. Often, however, it either follows or occurs in the course of such febrile diseases as typhoid, typhus, smallpox, measles, diphtheria, influenza, scarlet fever and gonorrhœa, malaria, and in association with cerebrospinal and other forms of meningitis. The disease in these cases may either be due to the toxins circulating in the blood as the result of bacterial activity, or to the local presence of the micro-organisms themselves. Other toxic agencies, such as vegetable poisons in ergotism and pellagra, and mineral poisons—*e.g.*, lead and arsenic—may cause myelitis.

In the vast majority of cases due to infection, myelitis is not localized to one particular level, but is disseminated, foci occurring in several regions.

**Acute Myelitis.**—The naked-eye appearances are variable. The spinal tissues are sometimes softened, pinkish-white in appearance, yellowish, or brownish-red, according to the condition of the blood-vessels and the amount and change in the extravasated red blood-corpuscles. In an early stage a large number of granular corpuscles and amyloid bodies appear; the axis cylinders are either swollen and granular or destroyed, and the myelin sheaths of the white matter are rapidly broken up. The ganglion cells undergo degeneration; their processes are swollen and varicose, or broken off; stained by Nissl's method, the chromatic substance loses its normal appearance, and the granules are no longer visible in the cell body or dendrons; the protoplasm is diffusely stained, and the nucleus excentric or extruded; later the cells present signs of atrophy, and eventually may completely disappear.

The *vessels*, thrombosis of which appears in many cases to be the determining cause of the above-mentioned changes, are engorged with blood, and their lymphatic sheaths filled with leucocytes; and

when the inflammation is very intense, hæmorrhages may be found. There is an increase of nuclei and small round cells in the grey matter, and spider-like neuroglia cells are more numerous than normal.

Later the connective tissue undergoes proliferation, and there is rapid progressive softening of the nervous elements, owing to granulo-fatty degeneration. The process thus passes into the chronic stage, constituting *grey softening*. Hæmorrhages may occur in those foci of softening, and eventually the process ends in a *sclerosis*, an overgrowth of fibrous connective tissue replacing the cells which have been destroyed.

All varieties of *diffuse myelitis* have a common pathological anatomy, but the clinical symptoms will of necessity vary according to the seat, extent, and distribution, of the inflammatory process.

**Meningo-Myelitis.**—In the early secondary stage of syphilis there occasionally occurs a focal meningo-myelitis, with local thickening of the meninges, and a diffuse peripheral myelitis, involving the white matter of the cord irrespective of any definite tract areas. In this condition the vascular changes are not those of ordinary syphilitic lesions, but consist of venous dilatation, and occasionally stasis, with a well-marked periphlebitis, while the arteries show no signs of syphilitic disease. A somewhat similar distribution of disease may occur in tertiary syphilis, resulting in replacement of the peripheral portions of the white matter by fibrous tissue and general contraction of the spinal cord. In such cases the vascular changes are similar to those in late syphilitic manifestations generally. Transverse myelitis is in the vast majority of cases a *compression* myelitis, produced by tubercular caries, tumours of the vertebræ and meninges, hypertrophic pachymeningitis, hydatid cysts, eroding aneurisms, fractures and dislocations of the vertebræ. The disease is seldom of any great vertical extent, and the secondary cord changes may affect a part or the whole of the transverse area of the cord, as in true myelitis. The spinal cord at the seat of the compression may be flattened, indented, or even reduced very greatly in size. On section it usually presents a greyish appearance. Microscopically the changes in the cord are much more marked in the white than in the grey matter as a rule. The nerve fibres, swollen axis cylinders, and dilated medullary sheaths, which stain badly with Weigert's hæmatoxylin, show marked degeneration when stained by Marchi's fluid. In advanced cases dilated spaces are left in the neuroglia, containing here and there broken-down débris of nerve fibres and compound granule cells, or neurophages. The pericellular lymph spaces and lymph sheaths of the bloodvessels are dilated, the latter containing leucocytes. In old-standing cases, sclerosis follows the localized cord changes, and ascending and descending degenerations occur. The above changes are due mainly to deficient circulation in the compressed

area, which is largely the result of venous and lymphatic obstruction. At the same time, in many cases where there is an associated toxæmia, the compressed area becomes a *locus minoris resistentiæ*, so that not infrequently true inflammatory manifestations are superimposed.

The pathological effects may be considered under two distinct headings—*root symptoms* and *cord symptoms*. The former usually develop first, in the form of *shooting pains*, owing to irritation of the sensory roots involved. With the pain there is usually *hyperæsthesia* of the skin. Irritation of motor roots causes *painful contracture*. *Cord symptoms* are—Paresis or paralysis below the lesion, *increase of superficial reflexes* and of *myotatic irritability*. There may be no loss of sensibility discoverable in the parts below the lesion, although there is complete spastic paralysis; indeed, in all cases of compression myelitis, the functions of the long motor tracts are much earlier and much more severely affected than the functions of the long sensory conducting tracts; but there may, on the other hand, be delay, and in severe cases absolute loss of sensation. Should the lesion become physiologically or anatomically completely transverse, there is necessarily complete loss of sensation below the lesion, associated with flaccid paralysis with complete loss of sphincter control. Paralysis of the sphincters and a tendency to bedsores accompany lesions affecting the lumbar enlargement. If the lesion is in the lower cervical region, the pupils may be affected from implication of the cilio-spinal centre, and the pulse-rate diminished from damage to the accelerator fibres of the heart.

**Poliomyelitis.**—Since we have gained knowledge concerning this disease, in which the whole cerebrospinal axis may be affected, the term, as Batten suggests, should be extended to polioencephalitis. It is sometimes called "infantile paralysis," because children are so frequently affected, yet the disease is by no means limited to children. The terms "Heine Medinische Krankheit" and "epidemic paralysis" have been used, but to both there are objections. The former tends to show that we have no clear conception of the disease; the latter indicates that the disease always occurs in epidemics. This is by no means the case, although the disease, occasionally in this country and generally in Scandinavian countries, assumes an epidemic form.

Poliomyelitis or polioencephalitis is a notifiable acute infective disease, having a special selective action on the nervous system. It gives rise to certain varied lesions in the central nervous system, and clinical symptoms in correspondence thereto. Such symptoms are, according to Batten: (1) A localized paralysis of groups of muscles affecting one or more limbs in part, or totally; (2) an ascending paralysis, frequently rapidly fatal, owing to involvement of the upper cervical spinal cord and phrenic centres; (3) an acute

ataxia ; (4) a paralysis of one or more cranial nerves ; (5) hemiplegia ; (6) the symptoms of meningitis ; (7) an acute mental defect ; (8) a type of case in which pain, especially on movement, is the most marked feature—so-called " neuritis."

The most common form of paralysis resulting from this disease is a paralysis of one or more groups of muscles of one leg or both legs, causing various forms of talipes to ensue. An excellent account of the epidemiology of this disease has been written by Batten, who also gives an account of the recent work that has been done on the nature of the virus. Landsteiner, Popper, Flexner, Levaditi, and Lewis, have published work showing that the disease is transmissible from man to monkeys by inoculation. The disease was conveyed to monkeys by inoculating the peritoneum with the spinal cord of fatal human cases, or by an inoculation into the brain or subcutaneous tissues of an emulsion of the cord from fatal human cases. The virus is not killed by glycerination, and it will pass through the finest filter. The organism has not been cultivated or seen under the microscope. The virus can be obtained from the mucous membrane of the nose of an infected monkey, and it has been shown to exist there as long as six months after the animal was inoculated. Animals living in the same cage with infected monkeys do not contract the disease ; it is only when the mucous membrane is injured that an animal can be infected. Some of the above-named observers have shown that when the virus is introduced into a nerve trunk it travels by the lymph spaces of the nerves and reaches the spinal segments at the entrances of the nerve roots, so that the paralysis always occurs on the side corresponding to the nerve trunk inoculated. Infection can be prevented from extending, by cutting the nerve above the point of inoculation. On experimental grounds, the period of incubation would be from five to six days.

**Morbid Anatomy.**—Cornil and Ranvier were the first to describe the pathological changes found in the spinal cord, but their cases were chronic, and do not, therefore, give a picture of the disease as it occurs in the acute stage. In the epidemic cases the membranes of the cerebrospinal axis are congested, and here and there small hæmorrhages may be seen. Upon section of the spinal cord, the grey matter of the anterior horns, and not infrequently the central and posterior grey matter, is softened and red, and swells up above the cut surface. Frequently the inflammatory appearances and hæmorrhages are more marked on one side than the other, and in one region more than another. The cervical and lumbo-sacral enlargements, especially the latter, show the most marked change as a rule, but the whole cord may be affected, and even the bulb.

In an acute case which was under his care and which died fourteen days after the onset of symptoms, Mott observed the following

microscopic appearances in the spinal cord: The bloodvessels were gorged with corpuscles; there were capillary hæmorrhages; there were leucocytes in great abundance throughout the inflamed tissue, and a great increase of neuroglia nuclei. The cell infiltration was so great in places as to obscure the nervous tissue. The ganglion cells, especially those of the anterior horns, but also those of Clarke's column, showed various degrees of chromatolysis or diffuse staining. The processes were either destroyed, attenuated, or swollen up. Sections, longitudinal and transverse, of the spinal cord in the lumbar enlargement, showed thrombotic occlusion of a branch of the artery in the anterior median fissure, going to the anterior horn of one side and a corresponding area of necrotic softening, with destruction of the ganglion cells. Later, as the inflammation subsides, the effects of the irreparable damage become manifest; consequently there is atrophy of the anterior cornua, with the disappearance of groups of cells corresponding to the motor innervation of groups of muscles. The appearances presented by the spinal cord may vary very considerably, according to the length of time which has elapsed since the onset of the disease. In an old case the segments of the spinal cord corresponding with the muscular paralysis (usually the lumbar and cervical enlargements) exhibit a more marked translucency of the grey matter of the anterior horns, and if limited to one side, as it often is, a diminution in size of the anterior horn as compared with the opposite healthy side. The anterior horn cells may be absent, or vestiges of degenerated ganglion cells, in the form of obtuse or rounded protoplasmic bodies without processes, may be present. The fine nerve plexus around the cells is either greatly diminished or completely absent, and only neuroglia and Deiters' cells may be visible. The vessels are thickened. When the lesion is bilateral, it is rarely symmetrical; more frequently it is unilateral, and it will then be observed that there is secondary atrophy of correlated structures of the same half of the cord—viz., of the posterior column, antero-lateral column, and posterior horn. Some observers have described atrophy of the corresponding motor convolutions of the brain. Atrophy of anterior root fibres must occur. Atrophy of the bones has also been found.

**Landry's Paralysis** (Acute Ascending Paralysis).—No definite lesion has been described in this disease. It may be due to the effects of a toxin acting upon the central or peripheral nervous system. The only changes revealed by careful post-mortem examination are varying degrees of chromatolysis of the motor cells of the medulla and spinal cord, and of the cells of Clarke's column. *The absence of troubles of nutrition and sensibility* points to the poison acting, like curare, especially upon the motor tract, and serves to distinguish the disease from acute myelitis.

### Congenital Defects of the Brain.

It is only possible in this section to consider those defects associated with congenital hemiplegia, diplegia, epilepsy, and imbecility.

Infantile paralysis of cerebral origin may be divided into two main classes: (1) Those in which paralysis is confined to one side (hemiplegic forms); (2) those in which the whole body is to a greater or less extent affected (diplegic forms). These are for the most part distinct pathological and clinical entities, and for the most part the former are post-natal, and due to gross destruction of cerebral tissue, either as the result of prolonged labour giving rise to cerebral hæmorrhage, or of encephalitis; while, on the other hand, cerebral diplegia is the result of primary degeneration of the nerve cells of the cerebral cortex, of which maternal morbid states are in all probability the potent cause. Heredity plays an important part, since this condition frequently occurs as a family disease, several children of the same mother often being affected, while this is practically never the case with infantile hemiplegia. Hereditary tendencies and parental diseases would seem to impart a diminished resistance and shortened tenure of life to the highly specialized cortical cells, which often, after a short period of apparently normal activity, begin to degenerate. This degeneration may begin during fœtal life, as in cases of congenital diplegia, Friedreich's ataxia, etc. In some cases such degeneration confines itself to particular systems of nerve cells, as in cases in which only the pyramidal systems are involved. Here the intellectual faculties largely escape, and there would seem to be every gradation from these simple types to the more severe types in which practically all the systems are involved—*e.g.*, amaurotic family idiocy. The appearance of the cerebellar and cerebral cortex in these cases of general cell atrophy is striking. Sulci are wide open, the convolutions stand out from one another and are very firm, while the surface of the convolutions shows that worm-eaten appearance so characteristic of atrophy. Microscopically there is a great paucity of the essential nerve elements in affected areas, and a corresponding increase of neuroglia tissue. The convolutional pattern may be quite normal, but if the atrophy has commenced very early in fœtal life, primitive forms of arrangement are met with. In cases where the central convolutions are prevented from developing by disease before the third month, there is no attempt later to form a pyramidal tract; but not only do parts directly connected with each other remain undeveloped, but also those parts which are physiologically interdependent. This is seen typically in cases where there has been an early degeneration of the frontal or temporal lobes, with almost complete absence of development of the opposite side of the cerebellum. Similarly, in some cases of deaf-mutes where the vestibular system is absent

owing to lack of development of the semicircular canals, the cerebellum may be found to be relatively small and undeveloped.

**Porencephalia** is generally congenital. It is a defect of the convolutions of variable extent, by which a cavity is formed, penetrating a variable distance into the hemisphere, sometimes even as far as the ventricles. The meninges are intact, and usually present neither thickenings nor adhesion; but at times the membranes are found adherent to the ependyma of the ventricles. It is of some significance that the defect is usually limited to the area of some definite vascular supply. The surrounding convolutions usually present a radiate appearance.

### Tumours.

The cause of cerebral tumours is, as in the case of tumours elsewhere, still a matter for speculation, excepting always those tumour-like tubercular and syphilitic masses and parasitic cysts which are usually considered under the heading of cerebral tumours, owing to the fact that they are clinically indistinguishable from true tumours.

Some of the growths met with in the central nervous system are identical histologically with those met with in other parts of the body, and these presumably arise from the meninges, bloodvessels, and their lymphatic sheaths (endotheliomata, sarcomata, etc.), while many are secondary deposits from growths elsewhere. There are, however, a large number of tumours, of which glioma is the commonest, which commence in the true epiblastic tissues, and have a structure peculiar to themselves, not met with in growths elsewhere. These, together with other primary forms, are probably the result of developmental causes as yet little understood.

Cerebral tumour is met with most frequently in early and middle life. It is of interest to note that, according to the statistics of the National Hospital, Queen Square, subtentorial tumours are much more frequently found in children than supratentorial, while the opposite is the case among adults. The greater number of subtentorial tumours in childhood are tubercular in origin.

Excepting syphilis and tuberculosis, the other forms of primary tumour may develop in otherwise healthy persons, although the history of a recent blow or injury to the head is obtained too frequently to be a mere coincidence. The causal relationship is difficult to see, but it may be that the blow excites inflammatory changes in the tissue around a growth more or less latent, and so hastens its progress.

**Gliomata** are most frequently found in the white matter of the central nervous system. They do not necessarily destroy the brain substance, and frequently the nerve fibres are pushed aside, and retain more or less their conducting power, or the fibres may be separated by infiltrating processes of the new growth. These infiltrating types are not infrequently found in

the brain stem, pseudo-hypertrophy of the pons being a typical example of a large infiltrating growth bringing about comparatively slight abrogation of function. The more compact gliomata are very poorly supplied with bloodvessels. Hence the central portions of the growth are extremely liable to undergo softening and other degenerations, with pseudo-cyst formation.

**Sarcomata** seldom arise in the substance of the central nervous system, being of mesoblastic origin. Primary sarcoma usually commences in the surrounding tissues—*e.g.*, in the pia arachnoid membrane, in the dura mater, in the cranial bones and vertebræ. Such bony tumours are most frequently found at the base of the skull.

**Endotheliomata** are fairly common as primary tumours of the nervous system. They arise from the endothelium of the arachnoid or of the lymph sheath of the small bloodvessels, and have a structure frequently resembling that of a carcinoma in its alveolar arrangement. They are usually circumscribed, and when slow-growing show comparatively little tendency to recur if completely removed. The most benign form is the fibro-endothelioma, which starts in the dura mater; it is slow in growth, and does not tend to infiltrate. These tumours are not very uncommon in asylum patients suffering from epilepsy and dementia; they may attain a large size, and when situated in the left frontal lobe they are sometimes mistaken for general paralysis.

**Gummata** are considered under Syphilis of the Nervous System.

**Tubercular Masses.**—These tumours are most frequently met with in children, their most common situation being below the tentorium in the cerebellum or pons. These masses are accountable for a majority of cases of cerebral tumour in childhood, and may lie latent for many years, death ultimately occurring in many cases as the result of the infection spreading to the meninges, and thus giving rise to tubercular meningitis.

**Carcinoma** is necessarily in all cases secondary to some tumour in a distant part of the body. Of all carcinomata, that affecting the mammary gland most frequently gives rise to metastasis within the central nervous system.

**Psammomata** as a rule do not produce symptoms of intracranial pressure, owing to their slowness of growth and comparatively small size, although they may give rise to Jacksonian epilepsy, and even general convulsions, when pressing upon the central convolutions.

**Parasitic Cysts.**—These include hydatids and cysticerci. The former are very common in certain countries, such as the Argentine and Australia, and when situated in the central nervous system there is little attempt on the part of the surrounding tissues to form an adventitial sheath. They are usually single,

and contain no daughter cysts. Hence their removal is a comparatively simple matter, and they are, perhaps, the most satisfactory type of cerebral tumour to treat. *Cholesteatomata, angiosarcomata, angiomata, dermoid cysts, cysts of the choroid plexus,* villous ependymal tumours growing within the ventricles, and of an adenomatous structure, sometimes occur.

**The General Symptoms of Tumour** are *headache, vomiting, vertigo, slow pulse, convulsions, stupor, drowsiness,* and, most important of all as a means of diagnosis, *optic neuritis.* All these symptoms are probably due to increased intracranial pressure. *Optic neuritis* depends not so much upon the size and situation of the tumour as upon the rapidity of its growth. There are three views as to the causation of optic neuritis—viz.: (1) that it is due to irritation and inflammation of the sheath of the optic nerve, produced either by irritation arising from substances contained in the cerebrospinal fluid of the sheath of the optic nerve, or by direct extension of meningitis; (2) that it is due to obstruction of the outflow of the venous blood from the ophthalmic vein, owing to the increased pressure on the cavernous sinus; but this theory of Von Graefe has been discounted by the fact that a free anastomosis occurs between the ophthalmic and facial veins; (3) that the intracranial pressure interferes with the return of lymph along the sheath of the optic nerve, causing œdema and swelling of the disc rather than a true neuritis. Gowers inclines to the opinion that a combination of causes may be in operation. No doubt simple stasis in the veins would soon be followed by exudation and migration of leucocytes, and all the appearances of inflammation might thereby be produced. In many cases of tumour, an ampullary swelling has been observed where the sheath is weak at the entrance to the eyeball.

**Regional or Focal Symptoms** are caused by either direct or indirect involvement of structures possessing particular functions. The morbid process may occasion phenomena of an *irritative* character—*e.g.*, a tumour situated in some part of the Rolandic region may produce unilateral convulsions—or it may be *destructive,* and produce loss of function (paralysis).

It is of great importance to remember that focal symptoms occurring late in cases of cerebral tumour with marked increase of intracranial pressure are worse than useless, and often extremely misleading, if it is attempted to utilize them as a means of localizing the position of the tumour. This is due to the fact that prolonged increase of intracranial pressure often leads to cranial nerve palsies quite independent of the position of the tumours. Again, the cortical anæmia produced by the pressure often gives rise to attacks of Jacksonian epilepsy or general convulsions. Not infrequently cortical thrombosis, or even hæmorrhage, due to vascular degeneration as the result of anæmia and pressure, may occur and give rise to varying degrees of monoplegia, aphasia, etc. From these

remarks it will be seen how futile it is to place reliance on late-appearing focal symptoms as true localizing signs.

**Syringomyelia.**—This is a *central gliosis* of the spinal cord, causing destruction of the grey matter and *excavation*. The usual seat is around the central canal in the *peri-ependymal* tissue, or behind the canal, in the grey substance of the posterior commissure; thence it invades the anterior and posterior horns. It is usually a neoplastic formation, but, according to Charcot, it may arise from a central myelitis. The cause of this active growth of embryonic tissue is unknown. The resulting symptoms are *muscular wasting* and *loss of sensation to heat and cold*, and *to painful impressions*, but preservation of sense of touch. This sensory dissociation is peculiarly characteristic of the disease, and goes to prove that Schiff was right in asserting that the grey matter conducts painful sensations, and the posterior columns tactile and muscular sense impressions. The destruction of the anterior horns produces the muscular wasting; that of the posterior horns, the sensory disturbance, and, *possibly*, the trophic affections that often occur. Of course, the distribution of the motor, sensory, and trophic changes will depend entirely upon the segments of the spinal cord affected. There may be unilateral destruction of anterior and posterior horns of the same side, and this has been found associated with motor paralysis and sensory disturbance of the same limb or side of the body (*vide* Fig. 9*B*).

## Disseminated Cerebrospinal Sclerosis.

The varying signs and symptoms of this disease are due to the formation of patches of sclerosis scattered in an irregular manner throughout the brain, spinal cord, and cranial nerves. (Fig. 9*A*). It usually attacks healthy subjects in early life, and seldom begins after the fourth decade. Since its exact cause is quite unknown, many morbid influences, such as grief, worry, overwork, etc., have been associated with the disease as causal agents. Not infrequently cases follow an acute specific fever, and accordingly it has been conjectured that the disease is due to some toxic action on the nervous system.

**Morbid Anatomy.**—Scattered at random throughout the brain, spinal cord, and not infrequently some of the cranial nerves and the roots of the cauda equina, are islets of sclerosis, varying in size from a hemp-seed to a walnut. The largest patches are to be found in the centrum ovale. The naked-eye appearance of these patches varies greatly with the stage of the disease. In the early stages the patches are only observed, in many cases, after the tissue is hardened in Müller's fluid, when they are seen to be much paler than the surrounding tissue. This fact probably accounts for many cases in which no changes have been observed at the post-mortem examination being classed as hysteria. In later stages the patches

# PLATE IV

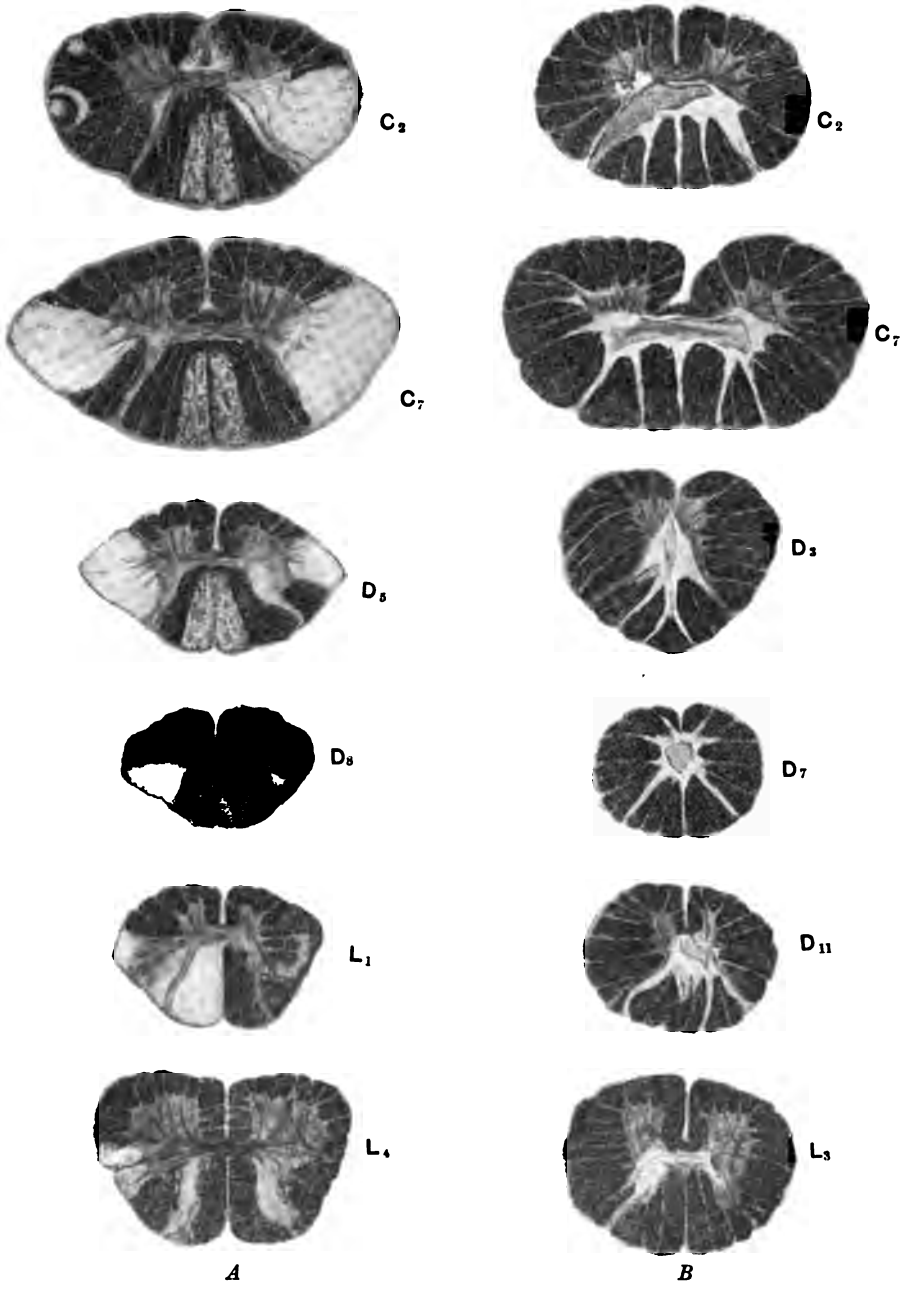


FIG. 9.—A SERIES OF SECTIONS OF THE SPINAL CORD, SHOWING : *A*, DISSEMINATED SCLEROSIS ; *B*, SYRINGOMYELIA.

*To face page* 408.

are not unlike gliomata, and present a greyish to greyish-white appearance, thus showing up in contrast to the white matter in which they are for the most part situated. Some patches have well-defined margins, while others shade off into the surrounding tissue. Occasionally the patches involve the grey matter of the spinal cord and brain stem, but the grey matter of the cerebral cortex is practically never involved. In the same case the consistency of various patches varies greatly, some being much softer, while others are harder, than the surrounding tissue. One of the most striking features of the disease is the absence of secondary degenerations above or below the lesion, even when a patch of sclerosis involves almost the whole transverse section of the spinal cord. This fact, which is explained by absence of complete destruction of the axons in the patches, readily distinguishes disseminated sclerosis from conditions of disseminated myelitis and disseminated syphilis of the nervous system, in which secondary degenerations are well marked. Microscopically the islets consist of a meshwork of neuroglia, in the meshes of which a great many neuraxons may be observed devoid of a myelin sheath. These neuraxons are not observed in Weigert preparations, owing to the absence of the myelin sheath, but can clearly be observed when stained by one of the silver methods. In very advanced patches very few neuraxons are to be seen; in most cases, towards the periphery of the patch, normal nerve fibres gradually begin to appear, but in some cases the transition is quite sudden. In early cases the patches are seen to contain dilated bloodvessels, surrounded by leucocytes, and to a lesser extent this is not infrequently seen in the periphery of older patches. The leucocytes are frequently seen to contain products of myelin-sheath degeneration. The question arises, Is this inflammatory reaction due to some toxin circulating in the blood, or is it simply a reaction set up by the products of degeneration of the myelin sheath? It is extremely difficult to answer this question, owing to the fact that cases seldom die presenting the earliest changes; but from the fact that acutely developing paraplegia, and at times hemiplegia, are common manifestations during the course of the disease, and that such paraplegias present all the signs of organic lesion due to blocking of impulses through the spinal cord at some definite segmental level, it seems more than probable that large patches of sclerosis are preceded by acute vascular dilatation and inflammatory œdema of the surrounding parts. The œdema is transient, and clears up with comparative rapidity, leaving behind it a patch of softening (so-called sclerosis). Many authorities suggest that these exacerbations of the disease are due largely to superimposed hysteria; but while it must be clearly recognized that hysterical manifestations are extremely likely to be grafted on to organic nervous disease, it is difficult to understand that a condition of almost complete

transverse lesion, with well-marked spasticity, sensory disturbances, and loss of sphincter control, can be the result of anything but an organic lesion. The earliest change to be observed in the neural elements proper is a swelling of the myelin sheath, which gradually breaks up, and is removed by the phagocytes. In the rare cases in which systemic degeneration occurs, it usually affects the pyramidal tracts. It has been suggested that the intentional tremors of this disease are due to the absence of the myelin sheath in the diseased patches, so that voluntary impulses are not insulated in their passage along the pyramidal tract. The ganglion cells situated in a patch of disease degenerate late, but eventually disappear, just as do the neuraxons. The mental changes associated with this disease vary greatly, and in some cases the only manifestation is a certain lack of emotional control, while in other cases not only is emotional control profoundly disturbed, but there may be considerable mental deterioration, with marked impairment of judgment and great loss of voluntary attention. Such mental changes can be explained by patches of sclerosis situated within the subcortical tissue causing dissociation of cortical centres. It must be clearly recognized that in all psychical processes the brain acts as a whole, and such action depends on the integrity of the association system of fibres. The amount of mental impairment may be said to vary directly as the involvement of subcortical association tracts.

### Cerebral Aneurism.

The causes of cerebral aneurism are the same as those of aneurism elsewhere, in so far as their underlying basis is, in the vast majority of cases, syphilitic arteritis and atheroma. But there is another important cause of cerebral aneurism, which is perhaps not so common in systemic aneurisms—viz., infective embolism. The arteries at the base of the brain are particularly prone to affection; especially is this the case with the basilar artery and its branches. The size of such an aneurism may vary considerably, but is very rarely larger than a pigeon's egg. Cases due to infective embolism are more commonly situated on the left side, and the carotid system is more affected than the vertebral. Rupture of such aneurisms is not an infrequent occurrence, the blood usually escaping into the membranes at the base of the brain, and in such cases the lumbar-puncture fluid is markedly blood-stained.

### Syphilitic Disease of the Central Nervous System.

Of all the single causes which lead to diseases of the nervous system, syphilis is unquestionably the most important. The *Treponema pallidum* has been found in congenital syphilitic lesions of the central nervous system by Ranke. The virus would seem to act

in three ways: (1) Directly on the bloodvessels, causing endo- and peri-arteritis and phlebitis, often leading to thrombosis with secondary degenerative changes in the nervous tissue; (2) gummatous infiltration may actually destroy and replace nervous tissue; (3) prolonged toxic action of the virus may interfere with and shorten the life-history of the neurones themselves, producing system degenerations, of which tabes dorsalis and general paralysis are by far the most common examples; but probably many cases of amyotrophic lateral sclerosis running acute courses are syphilitic in origin, and many cases of imbecility and epilepsy are due directly or indirectly to the virus of syphilis.

Syphilitic inflammation of the arteries and veins plays an extremely important part in the pathological anatomy, and certain vessels are much more commonly affected than others. This is especially seen in the vessels at the base of the brain, and to a lesser extent in the vessels of the Sylvian fissures. The specific inflammation of the vessels frequently leads to vascular occlusion, either directly by cell proliferation, causing an obliterative endarteritis, or, more frequently, by a secondary thrombosis of the diseased vessels. Not infrequently syphilis leads to a local or general inflammation of the membranes, which may be thickened and matted together (gummatous meningitis). In severe cases this meningitis may extend throughout the whole cerebrospinal axis, while in other cases multiple gummata varying greatly in size may be scattered on the surface or in the substance of the brain. These forms of cerebral syphilis may produce most varied symptoms. Partial or complete vascular obliteration in cutting off the blood-supply in various areas of the brain may lead, if incomplete, to temporary loss of function of the area involved; but if there is total occlusion, there is a resulting softening, unless neighbouring vessels afford a compensatory blood-supply. However, diseases of the arteries alone may long exist, without any symptoms of cerebral irritation or increased intracranial pressure. When the inflammatory process affects the membranes, the vessels are usually more or less affected also, and those entering the cerebral cortex from the pia mater are frequently surrounded by collections of lymphocytes and plasma cells. Thus, combination effects are frequent, and the results of vascular occlusion and cerebral softening may be associated with cortical irritation and cranial nerve palsies from gummatous infiltration of the meninges. The irritative phenomena vary with the situation of the gummatous infiltration, but usually include *severe headache*, which is worse at night, and not infrequently *vomiting* and *convulsions*. Owing to the great frequency with which gummatous infiltration affects the base of the brain, cranial nerve palsies are of very frequent occurrence; indeed, a partial or complete oculo-motor paralysis is present in the majority of cases of cerebral syphilis. There is practically

no limit to the time at which syphilitic disease of the nervous system may exhibit itself after infection, cases occurring as early as three months and as late as twenty-five or even more years after. It was formerly held that syphilitic disease of the nervous system was essentially a tertiary lesion, but more careful records and examination show that it *most frequently occurs within the first two years after infection*, and that the frequency of its occurrence diminishes with each successive year. Exciting causes of cerebral syphilis may be traumatism, exposure to the sun, excitement of various kinds, sexual excesses, and over-indulgence in alcohol; but the most potent factor is lack or insufficiency of specific treatment.

Congenital syphilis may be associated with exactly similar changes in the central nervous system.

**Morbid Anatomy.**—The mesoblastic structures of the cerebro-spinal axis are attacked by the syphilitic virus, which brings about a round-celled infiltration of the membranes, which may form a superficial gelatinous layer or deposit. When of recent origin, this membranous deposit may be removed with the finger, but when of some standing it is dryer and firmer, and may be studded with multiple small nodules. This round-celled infiltration may extend from the surface into the brain substance along the course of the vessels, which are seen to be surrounded by either gummatous tissue, or, in other places, the perivascular lymphatic sheath may be distended with lymphocytes and plasma cells. Again, the process may extend into the fissures, filling them with a gummy mass. Gummata probably do not start primarily in the substance of the brain, but are rather extensions of neoplastic formation along the vessels from the surface. The membranes affected may be thickened locally or generally, the appearance depending largely upon the age of the process. When the process is of recent origin, the inflammatory deposit is soft and gelatinous, opalescent, greyish-red or yellowish in appearance. In such cases it is practically impossible to decide without microscopical and bacteriological examination whether the condition is tubercular or syphilitic. If the disease is long-standing, the inflammatory process may have gone on to the formation of scar tissue. When the granulation tissue forms a definite tumour mass, either on the surface or in the substance of the brain, a gumma, as distinguished from gummatous meningitis, results. Such tumours may vary in size from a grain of wheat to a walnut.

**Gummata** are particularly common about the base of the brain, especially in the neighbourhood of the optic chiasma; but they may occur in any region, being scattered in rare cases in the walls of the veins and arteries, and not infrequently involving the dura mater; while in some rare cases the skull may be eroded, and a gummatous mass, which originated in the dura, may project externally. The vessels present irregular, greyish-white nodules, which are usually

unilaterally situated, so that when cut across these nodules present a half-moon appearance. Such vessels usually feel firm and cartilaginous between the fingers, and do not easily collapse on pressure. When there is universal arteritis, the vessels appear opaque and dirty white in colour, and their walls are much thickened. In severe cases the veins show similar changes, but to a lesser degree. The fact that such vascular changes are so common about the vessels at the base of the brain is probably accounted for by their being constantly bathed in an excess of cerebrospinal fluid, which probably contains the virus and products of disordered metabolism set up by its action.

**Microscopical Appearances.**—Syphilitic arteritis is partly an endarteritis and partly a periarteritis, characterized by proliferation of the endothelial cells and subendothelial tissue of the intima. It generally affects one side of the vessel more than the other, but the whole intima may be equally involved. Periarteritis is almost equally characteristic, and the adventitial and periadventitial tissue is usually infiltrated with round cells and plasma cells. The inner coat is thickened, owing to the development of spindle-shaped and stellate cells. These do not usually undergo caseation, but should they do so, there results a patch of atheroma. As will be seen, there is nothing actually specific in the process described, but it is strong presumptive evidence of syphilis when one finds irregular thickening of the intima which has not undergone caseation. Occasionally there may be a new formation of capillaries associated with the process, and these may penetrate into the intima. Where there is actual gummatous formation in the walls of the veins or arteries, such formations are situated in contradistinction to the infinitely more common arteritis in the middle or outer coats. Actual thrombosis of the diseased vessels is of frequent occurrence, and subsequent organization of the clot may occur, eventually converting the vessel into a fibrous cord.

While thrombosis is common, vascular rupture is rare, and aneurism is a very occasional occurrence. Accordingly the important clinical result of syphilitic arterial disease is cerebral softening. The vessels lying within the Sylvian fissures are very commonly affected; hence the symptoms due to cerebral softening can in many cases be traced to the involvement of the middle cerebral artery or some of its branches in the thrombotic process.

### Cerebral Softening.

The most common causes leading to this condition are thrombosis and embolism.

**Softening from Thrombosis.**—This is in the majority of cases the result of atheromatous, calcareous degeneration, or syphilitic disease of the arteries of the brain. As a result of the cutting off of

its blood-supply, the area of nervous tissue involved undergoes a more or less rapid necrosis. Thrombosis may be either arterial or venous. In the latter case the sinuses are most frequently involved. Such sinus thrombosis may be primary (marantic) and non-infective in character, occurring in conditions of asthenia after prolonged illness—*e.g.*, after typhoid fever—or in conditions associated with low arterial pressure and heart failure. Secondary thrombosis may be the result of extension of the thrombosis along a vein from some adjacent part—*e.g.*, the orbit—secondary to which thrombosis of the cavernous sinus not infrequently results. Or, again, it

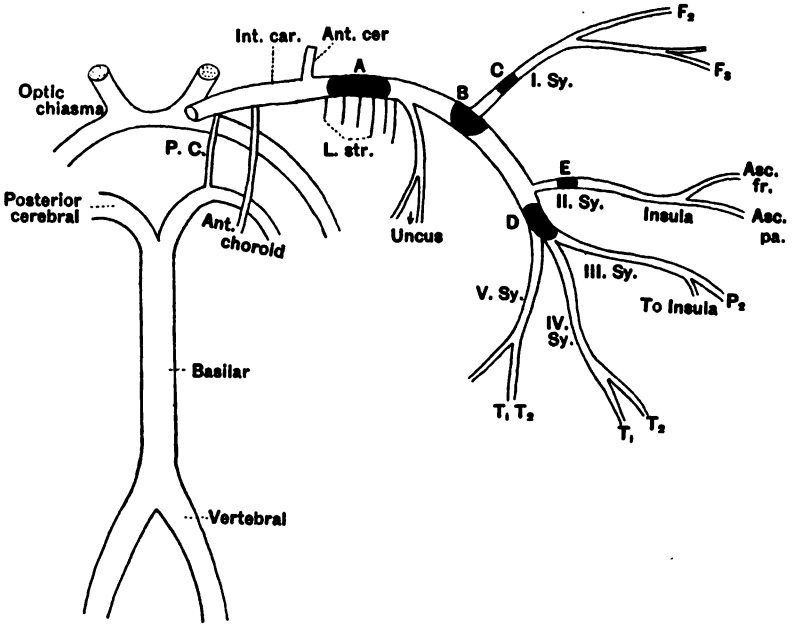


FIG. 10.—DIAGRAM (AFTER VON MONAKOW) TO SHOW THE EFFECT OF EMBOLISM.

may be the result of infection from some neighbouring tissue. As a common example, thrombosis of the lateral sinus is not infrequently seen in cases of middle-ear disease. Such sinus thrombosis causes great distension of the veins which open into it, and a secondary œdema not infrequently associated with small hæmorrhages in the area drained by these veins. More or less softening of the cerebral tissues thus affected is observed, mainly as a result of impaired nutrition. Arterial blockage may affect the white areas of brain tissue. Thus, if the middle cerebral artery be blocked at its commencement, there will not only be softening of the whole cerebral cortex involved, but simultaneously *the internal capsule*

*and basal ganglia* will be affected, resulting in *hemiplegia, hemi-anæsthesia*, etc.; and if on the left side, there will be *aphasia, word-deafness*, and *word-blindness*. If the artery be blocked at *B* beyond the basal arteries, there is a possibility of some collateral circulation being restored by the anterior cerebral. If the *first* Sylvian branch is blocked (*C*), there will be *softening in Broca's convolution* and *aphasia*. If the second (*E*), there will be *softening of the Rolandic area* and *hemiplegia*. Such hemiplegia is associated with more or less apraxia of the non-paralyzed side, due to softening of the posterior portions of the frontal convolutions, in which the highest motor centres are situated, this area on the left side dominating the Rolandic regions on both sides; while blockage of the posterior main division (*D*) of the middle cerebral on the left side causes word-deafness and word-blindness, paraphasia, astereognosis, varying degrees of ideational apraxia, etc., but not true motor aphasia or hemiplegia. The effect of occlusion of the posterior cerebral artery is lateral homonymous hemianopia, which is seldom complete, owing to the fact that the macular region is bilaterally represented.

**Softening from Embolism.** — The softening resulting from embolism is for the most part entirely dependent upon the obstruction to the circulation caused by the embolus and by the resulting thrombosis. It is rapidly induced, and is often attended by the extravasation of blood in its neighbourhood, when it constitutes one form of *acute red softening*. If the interference with the circulation be slight, and there be no extravasation of blood, the softened portions are white in colour. The vessel most frequently blocked is the middle cerebral artery, and in the majority of cases it is that of the left side. In almost all cases in which softening of the cerebral substance results from embolism, it is due to arrest of the embolus in one of the vessels *beyond* the circle of Willis, because here the circulation cannot be readily restored by the collateral vessels. Softening, however, does not necessarily follow the blocking of a cortical artery, for communication between these branches is freer than is often supposed.

It is a matter of considerable importance whether the detached fragment which gives rise to embolism carries infective organisms. If it does, not only is the vessel blocked by the embolus, but an infective inflammation of the arterial wall at the seat of obstruction occurs, with softening of the coats and formation of an aneurism, which may subsequently burst, so that a patient suffering from ulcerative endocarditis may die from hæmorrhage a short time after embolism of a cerebral artery.

**Morbid Anatomy.**—The results of embolism and thrombosis are essentially the same. The arterial blood-supply is cut off, and there is anæmia of the area supplied by the artery. For the first twenty-four hours there is only a slight change in the appearance

and consistence of the part, although the neurones may show microscopically well-marked histochemical changes. The affected area has generally a pale appearance; sometimes the capillaries may become distended by a backward flow of blood from the veins, and, giving way, produce small hæmorrhages into the perivascular lymphatics. Later on the tissue breaks down and softens, owing to imbibition of cerebrospinal and serous fluids by the dead tissues. When very little blood returns from the veins to the capillaries, the area of softening remains *white*; it is *red* when blood does regurgitate from the veins, especially when the wall of the capillaries gives way, allowing the red corpuscles to escape. Since the grey matter is far more vascular than the white, *red softening* is generally seen in the cortex and basal ganglia. *Yellow softening* is merely a later stage of the red, owing to alterations in the blood-pigment.

Microscopically the softened mass consists of myelin drops, swollen and degenerated nerve fibres, altered nerve cells, and granular corpuscles of Glüge, with free fat granules. These granular corpuscles, which may measure as much as 30 $\mu$ in diameter, are leucocytes distended with fatty débris.

If the circulation be re-established within a short time, the nervous structures do not necessarily die; but regeneration is impossible if necrosis has commenced. Resorption of the dead tissue is gradually brought about, with eventual formation of a *cyst*. If the area is small, a *scar* of fibrous tissue may be the sole indication of the destruction that has taken place. The convolutions of the cortex may sometimes be seen atrophied and *sclerotic*, especially in senile atheroma, and on tearing off the thickened pia arachnoid they present little erosions of a rusty-yellow colour. Sometimes portions of the convolutions, or even a whole lobe, may have entirely disappeared, and the space be occupied by a serous fluid enclosed by the thickened pia arachnoid membrane.

### Cerebral Hæmorrhage.

Cerebral hæmorrhage is the most frequent cause of hemiplegia after the fourth decade, and unless Bright's disease or some form of contracted kidney be present, with its associated high blood-pressure, or a cerebral aneurism ruptures, it is very rarely that hemiplegia, occurring early in life, is due to hæmorrhage. It has long been recognized that the vast majority of cases dying of cerebral hæmorrhage have kidneys the cortex of which presents a varying amount of sclerosis and contraction, associated with an adherent capsule, which when removed leaves a regular, granular surface. Such a condition is invariably associated with a considerable degree of arterio-capillary sclerosis, and to the constriction of the arterial tree thus induced the high blood-pressure is largely due. In all probability, in such

cases the arteriolar disease is primary, while the changes in the renal cortex are largely secondary to the disease in the small vessels which supply it. It is of extreme importance to remember that the underlying basis in this condition is the general arterial disease, and that the renal changes are seldom far enough advanced to cause death from renal inadequacy, since the patient usually succumbs from the direct or indirect effects of his arterial degeneration and high blood-pressure, either as the result of left heart failure or cerebral hæmorrhage.

For our purpose we are only concerned with the results of the vascular disease and high blood-pressure which present themselves in the central nervous system. Many of the small vessels entering the substance of the brain show minute miliary aneurisms. They are round- or spindle-shaped, and are caused by degenerative changes in the intima, being associated with atrophy and sclerosis of the media. The weakened vessel walls, having thus lost their elasticity, dilate with the increased blood-pressure. Miliary aneurisms are most frequently observed in the regions where hæmorrhage most frequently occurs. The arteries, however, which supply the region of the internal capsule—namely, the lenticulo-striate and lenticulo-optic—are particularly liable to disease and rupture. This is probably owing to the fact that they are end-arteries possessing no anastomoses. Another reason why cerebral vessels are more frequently the subject of miliary aneurisms than small vessels elsewhere is that they are comparatively unsupported by the substance of the brain, being surrounded by a perivascular lymphatic sheath. Other conditions which predispose to cerebral hæmorrhage are plumbism, alcoholism, and syphilis. Hæmorrhage either into the substance or in the neighbourhood of cerebral tumours is not infrequent, and in some cases may be the first indication of the presence of intracranial disease.

**Meningeal Hæmorrhage** is a frequent cause of birth palsies, and is due in the vast majority of cases, not to injury as the result of instrumental delivery, but rather to the rupture of one or more veins during difficult and prolonged labour. In general paralysis, and less frequently in senile dementia, subdural, subarachnoid, and subpial hæmorrhages are not infrequently seen, but have become much less common in recent years, with the more careful management of patients. Similar hæmorrhages are occasionally seen in various blood-diseases, and in very rare cases primary hæmorrhage into the ventricles of the brain may occur as the result of rupture of a vessel of the choroid plexus.

The effects produced by cerebral hæmorrhage depend entirely on its size and position, but, owing to the fact that the majority of such cases are due to rupture of a miliary aneurism of the lenticulo-striate artery, which supplies the motor portion of the internal capsule, the clinical picture presented is fairly uniform, consisting

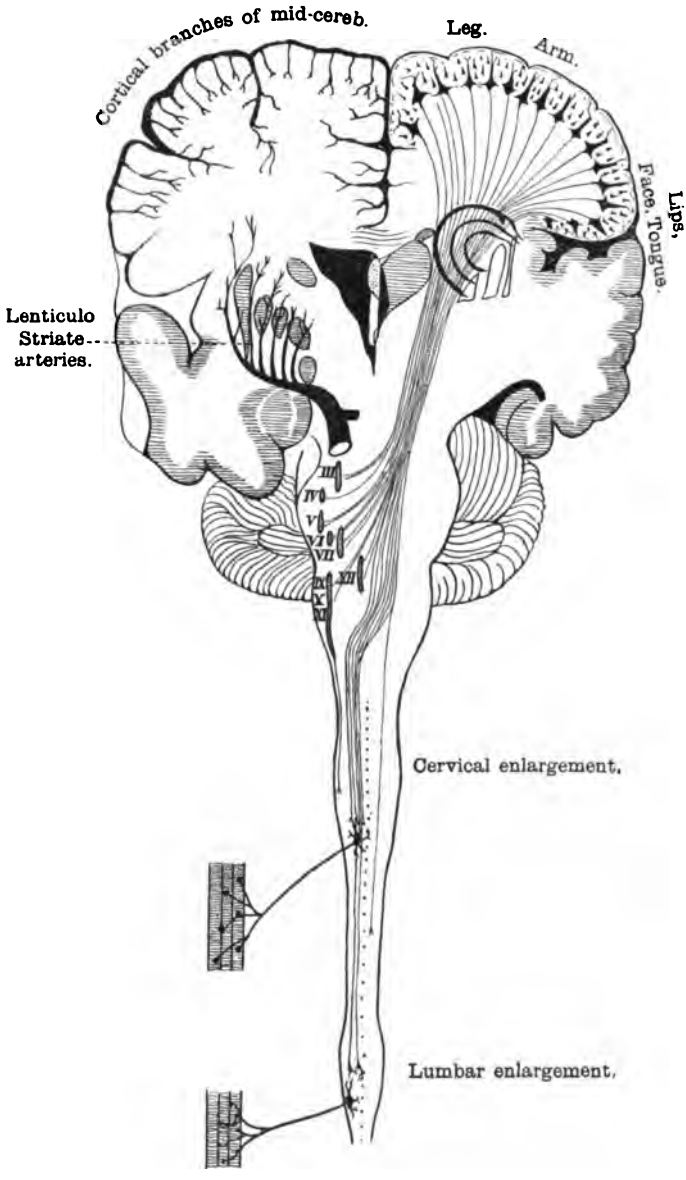


FIG. 11.—DIAGRAM TO SHOW THE DISTRIBUTION OF THE LENTICULO-STRIATE ARTERIES.

Branches of the middle cerebral, rupture of an aneurism on one of which is the frequent cause of apoplexy. It will be seen that as the blood effuses and lacerates the brain tissue to escape into the lateral ventricle it will destroy successively the axons of the cortical pyramidal neurones as they descend downwards to the motor nuclei in the pons, medulla, and cord, giving rise thereby to hemiplegia.

in a spastic hemiplegia, with the arm more affected than the leg, lower facial palsy, and articulatory difficulty. In the majority of cases the destruction caused by the hæmorrhage does not extend far enough back in the posterior limb of the internal capsule to give rise to more than slight and transitory sensory disturbance. If the lesion be not severe enough to cause death, various changes occur in the effused blood and damaged nerve tissues. For the first few days the clot fills the whole cavity, and does not undergo shrinking; then a fatty degeneration takes place, with absorption of the products. In recent cases the effused blood is dark in colour, generally clotted, and often mingled with lacerated brain substance. As changes take place in the blood, the colour alters first to a chocolate-brown, and later to a brownish-yellow.

The hæmorrhage is usually single, but when small there may be more than one. Sometimes evidence of a previous hæmorrhage is found in another region, in the form of a cyst, with orange-yellow staining of the walls and adjacent brain substance, or there may be a scar of connective tissue formed. In severe cases of hæmorrhage causing death, irruption of blood may take place, not only into the lateral ventricle of the same side, but also through the foramen of Munro into the opposite lateral ventricle. Occasionally it may find its way from the third ventricle through the aqueduct of Sylvius into the fourth ventricle, and, in rare cases, thence through the foramen of Magendie into the subarachnoid space.

### Degeneration of Efferent Tracts.

Under this heading the diseases which present themselves for brief discussion are known as *primary lateral sclerosis*, *progressive muscular atrophy*, and *amyotrophic lateral sclerosis*. In all probability the above conditions form a clinical entity, and are due to one and the same pathological process affecting different parts of motor apparatus. In the first the lateral columns of the spinal cord, and with them the Betz cells of the precentral convolution, are alone affected; in the second only the cells of the final common motor path (anterior horn cells) and the peripheral nerves are degenerated; while in the third both segments of the motor path are affected. Both clinically and pathologically intermediate cases combining the symptoms of all groups in different parts of the nervous system are frequently observed. Hence the conclusion is forced upon us that all these cases belong to one diseased condition.

**Primary lateral sclerosis** is due, probably, to retrogressive degenerative changes occurring in the Betz cells of the cerebral cortex, and their prolongations through the brain and cord as the pyramidal tracts. In other cases there is evidence of vascular occlusion and old softening in the region of the lateral columns.

In such cases the degenerative changes and often complete disappearance of the Betz cells might be entirely due and secondary to the pyramidal fibre destruction, while in other cases the degeneration of the pyramidal tracts would seem to be secondary to primary degeneration of the Betz cells.

In **progressive muscular atrophy** and **amyotrophic lateral sclerosis** the lesion of the lower motor segment is usually most marked. In the former the change begins in the anterior horn cells, usually in the cervical region, and is of the nature of a chronic anterior poliomyelitis, with associated degeneration in the corresponding motor nerves and the muscles which they supply. However, the upper motor neurone seldom entirely escapes, and if the atrophy of the anterior horn cells occurs early and is widespread, the signs of upper motor neurone involvement, as elicited by examination of the upper limbs, are often masked. On the other hand, in *amyotrophic lateral sclerosis* the signs of upper motor neurone involvement often dominate the clinical picture. Especially is this so in the case of the lower limbs, where spasticity, associated with exaggerated tendon phenomena, ankle-clonus, and extensor big-toe reflex, indicate a degeneration of the pyramidal tracts. Even in typical cases of this condition the wasting of the arm muscles may be advanced enough to obscure signs of spasticity which would otherwise be present. In *progressive muscular atrophy* several different types of the disease are well recognized, according as the chronic anterior poliomyelitis in the initial stages of the disease affects one part of the central nervous system or another. Sometimes the wasting begins in the small muscles of the hand; again, it may begin in the muscles of the shoulder girdles. The same broad distinction holds in the case of the legs, while in other cases the process may begin in the nuclei of origin of the cranial nerves, causing disturbances of articulation, phonation, deglutition, etc. (bulbar paralysis).

**Morbid Anatomy.**—Examination of the spinal cord shows more or less sclerosis and degeneration of the crossed and uncrossed pyramidal tracts and of the anterior root zone. In some cases the changes in the pyramidal tracts cannot be traced through the brain stem, while in the majority of cases they become less marked as the seat of origin of the fibres is approached. These facts lend support to the view that the disease is really an abiotrophy, the parts of the fibre farthest from their cell of origin degenerating first. However, in many cases the degeneration can be traced to the internal capsule of the cortex, and the Betz cells are greatly diminished in numbers; those present usually show considerable signs of disease, being irregular in shape, and presenting chromatolysis and marked excentricity of their nuclei. In contradistinction, the large pyramidal cells of the cortex, together with the association and tangential fibres, would seem to be quite normal.

Although the sensory disturbances in this disease are usually

very slight or entirely absent, there are not infrequently to be observed degenerative changes in the posterior columns, and in the direct cerebellar and Gower's tracts, notwithstanding the fact that Clarke's column and the cells at the base of the posterior horn are usually normal. The grey matter of the anterior horns is wasted and greatly deficient in fibres and cells. The large multipolar cells that remain are shrunken, and their processes broken off; in some cases only a little mass of pigment remains. The glia tissue is increased, and Deiters' cells are very numerous. The regions of the cord affected vary in different types of cases; *e.g.*, when the small muscles of the hand are atrophied, the anterior horns are atrophied in the lower cervical and upper dorsal regions. In the amyotrophic form the process commences in the upper pyramidal segment of the motor path. There are, therefore, exaggerated deep reflexes, accompanied or followed by a progressive and characteristic wasting of groups of muscles, owing to degeneration of the anterior horn. The peripheral nerve fibres corresponding with the atrophied spinal motor neurones are atrophied. The muscles are much wasted, and in extreme cases can hardly be distinguished from the surrounding fat; but in slight cases they are only pale. Examined microscopically, the fibres are seen to have lost their striation, and many show fatty degeneration.

### Combined Scleroses.

**Ataxic paraplegia** and subacute combined degeneration of the spinal cord are conditions in which a combination of the symptoms of lateral sclerosis and ataxy are present. For the most part, little is known concerning the cause of these conditions, except when they occur during the course of pernicious anæmia, pellagra, and rarely in diabetes.

**Morbid Anatomy.**—In the former disease the appearances of degenerative atrophy in the posterior columns of the cord closely resemble those of tabes, except that the posterior root zone is much less affected. A similar change is present in the lateral columns, especially in the crossed pyramidal tracts, but in the majority of cases the direct cerebellar tracts are also involved.

Subacute combined degeneration of the cord is in reality a multiple focal disease with secondary systemic degenerations. The focal lesions commence with swelling of the medullary sheaths of the nerve fibres; these gradually degenerate, and are absorbed, with total disappearance of the neuraxons, in contradistinction to the persistence of the neuraxon in the focal lesions of disseminated sclerosis. These focal lesions necessarily give rise to secondary degenerations. In early cases spaces may be seen where the nerve fibres have been absorbed, but in later stages the neuroglia has proliferated, and the tracts are replaced by sclerosed tissue.

**Friedreich's Disease.**—This is a rare disease, often affecting several members of the same family, beginning in the majority of cases between the fifth and fifteenth years. It may be looked upon as a neuronic abiotrophy affecting in a greater or lesser degree the whole kinæsthetic system, from the periphery to the cortex, although in some cases the changes in the peripheral nerves are relatively slight. There is an associated atrophy of great numbers of the Betz cells, and Mott has suggested that this is really secondary to the absence of stimulus in the cortical sensory receiving-station.

**Morbid Anatomy.**—Macroscopically the most striking characteristic is the smallness of the spinal cord, and to a lesser extent of the cerebellum and brain stem, which relatively to the rest of the brain weighs much less than normal. The posterior roots are for the most part atrophic, thin, flattened, and greyish-white in colour. The posterior columns show a degenerative atrophy and sclerosis, but the fine fibres of Lissauer's tracts are for the most part unaffected, in contradistinction to tabes; similarly, the fine fibres of the posterior roots are still intact, while the coarse fibres are degenerated. All cases show degenerative atrophy of the cerebellar tracts, while Clarke's column cells are for the most part entirely destroyed. A considerable number, however, show no changes, or comparatively slight ones, in the crossed pyramidal tracts, while in others even the coarse fibres of the peripheral nerves are undegenerated. It is probable, therefore, that the disease commences as a primary atrophy of the intraspinal terminals of the kinæsthetic proto-neurones, and that later the posterior roots and the peripheral nerves are involved. The neurones, consisting of small cells and fine fibres which subserve cutaneous sensory and viscero-vascular functions, are in great part spared, in contradistinction to tabes. Hence the absence of visceral and cutaneous sensibility disturbances, which are so common a feature of tabes.

## Parasyphilitic Diseases.

Under this heading general paralysis of the insane and tabes present themselves for discussion. It is now generally accepted that there is a very definite relationship between syphilis on the one hand, and tabes and general paralysis on the other. All carefully-compiled statistics point very strongly to this causal relationship. In cases where the attempt has been made to inoculate patients suffering from general paralysis with the syphilitic virus, the results have been negative. Another all-important link in the chain of evidence is the fact that in both conditions, if the disease is active, a positive Wassermann reaction is obtained. One of the strongest arguments that syphilis is the great causal agent of tabes and general paralysis is the existence, in both cases, of a juvenile form of the disease, occurring in the subjects of congenital syphilis, many cases of which have been

recorded by Mott. Other factors, such as worry, mental strain, overwork, sexual excesses, alcoholism, mental excitement, act only as exciting causes.

There are three main theories as to the relationship between syphilis and these diseases: (1) That the syphilitic organism is in itself the active causal agent; (2) that there is produced in the body as the result of syphilis a toxin, and that this post-syphilitic toxin is the cause of tabes; (3) that syphilis produces an impairment of the nervous system, and so predisposes it to degenerations from autotoxin and other causes, which would produce no effect on the healthy nervous system. The changes in the central nervous system in these diseases do not resemble those of true syphilitic lesions. Again, antisyphilitic remedies do harm rather than good in these conditions. Hence the justification of the term "post-syphilitic" or "parasyphilitic," which is now generally applied to them.

**Tabes Dorsalis.**—This disease is due to a primary progressive degeneration of the first proto-neurones of the central nervous system, and by this degeneration peripheral sensations are cut off from various parts of the central nervous system, the most obvious changes being degeneration of the prolongations, within the spinal cord, of the posterior root ganglia. Accordingly, the most striking lesion is that of the posterior columns. The clinical phenomena vary considerably in different cases, according to the main incidence of the degenerative process and its rapidity of progress.

**Morbid Anatomy.**—The pia arachnoid presents a varying degree of thickening over the posterior aspect of the cord, which is flattened and of a greyish colour. Many of the posterior roots are seen to be small and atrophic, and of a similar grey appearance to that of the posterior portion of the spinal cord. The cord on transection shows a well-marked contrast between the greyish-red atrophic posterior columns and the pearly-white lateral and antero-lateral columns. The degeneration is usually much more obvious in the lumbar and lumbo-sacral regions, and, correspondingly, the sensory roots of the cauda equina are more markedly atrophied than is elsewhere the case. Not only do the afferent projection systems of the spinal nerves degenerate, but frequently those of the cranial nerves also. This is especially so in the case of the optic nerve, the grey atrophy of which is so frequently a clinical manifestation of this disease. In advanced cases the peripheral nerves exhibit degenerative changes in a more or less marked degree. The degeneration seen in the posterior columns is in early cases of entirely exogenous origin, and is of exactly the same nature and distribution as that produced by section or disease of the posterior roots, as seen not infrequently in cases of tumour of the cauda equina. But in late cases with very marked ataxia the endogenous association tracts are also degenerated. The fibres which make

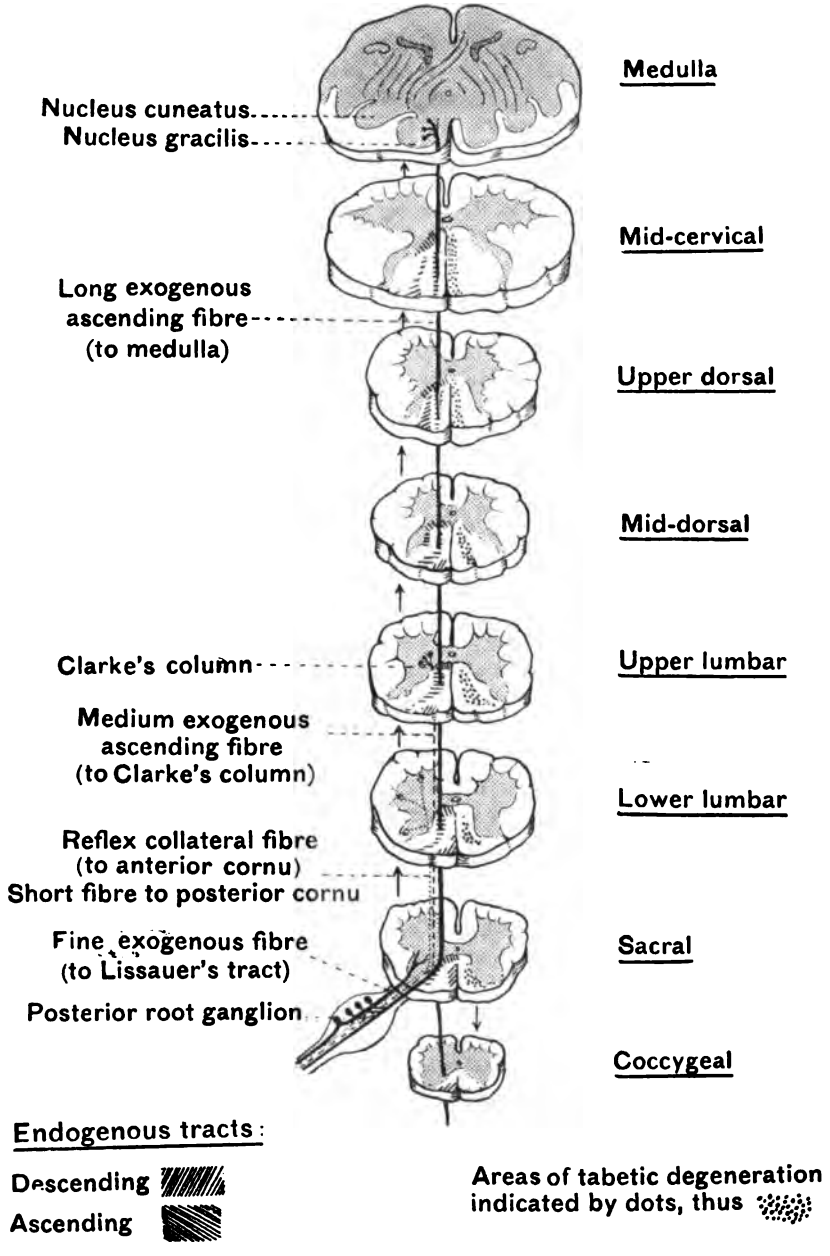


FIG. 12.—DIAGRAM TO SHOW ENDOGENOUS DESCENDING AND ASCENDING TRACTS. (AFTER FERRIER.)

up the posterior columns are derived from two sources: (1) The above-mentioned exogenous fibres derived from the posterior root ganglia; (2) endogenous fibres derived from the cells of the grey matter of the spinal cord, and passing mainly between one level of the spinal cord and another, thus bringing these various levels into associative connection one with another. Such fibres pass mainly between cervical and lumbo-sacral regions, some ascending and some descending. The early degenerative process of tabes affects only the exogenous system of fibres. Accordingly, Flechsig's oval area and the comma tract of commissural fibres present a more or less normal appearance in the midst of the degenerated exogenous fibres. This selective degeneration within the posterior columns would be hardly possible if the disease were due to sclerosis of the bloodvessels and altered blood-supply of the posterior columns; and, again, the overgrowth of neuroglia tissue cannot be other than secondary to, and a replacement of, the degenerated neural elements. The changes within the cord are for the most part symmetrical, and in the majority of cases the earliest and most advanced changes are in the lowest part of the cord, as would be expected clinically, since the ankle-jerk usually disappears a considerable time before the knee-jerk, and before the ataxic symptoms become manifest. However, there are occasional cases in which the earliest and main incidence of the degeneration is in the cervical region—*i.e.*, arm tabes. Visual defects are common, and are due to a similar degeneration of the fibres of the optic nerve; and in certain cases complete atrophy and total disappearance of the neural elements occur, leading to total blindness. Certain areas of the posterior columns degenerate earlier than others. This is especially seen in the posterior root zone, and to a lesser extent in Lissauer's zone, which is composed of fine fibres, forming a cap to the posterior root.

In such an early case, where there is no active disease of the posterior root fibres in the cervical region or dorsal region (*i.e.*, where during life there has been no comparative anæsthesia of cervical or dorsal segments), a transverse section of the cord above the dorsal region simply shows an ascending degeneration in the columns of Goll. It is of great importance to remember that the primary afferent proto-neurones, which arborize round the corresponding anterior horn cells (forming the first arc of the central nervous system), and round the cells of Clarke's column (forming the first link of the second or cerebellar arcs of the central nervous system), are similarly degenerated. Hence largely the disappearance of the deep reflexes and the interference with equilibration. Changes are very often present in the cutaneous nerves, and especially in the deep nerves from the body musculature and bones. These changes may be very marked, and complete atrophy may be extensively present in such cases where painless

perforating ulcers and destructive joint changes (Charcot's joints) occur.

Microscopical examination of the spinal cord shows the myelin sheath of the nerve fibres diminished or destroyed; the axis cylinder process may be swollen in one place, attenuated in another, and generally irregular in thickness or completely atrophied; the neuroglia is increased at the expense of the parenchyma, and there are a large number of Deiters' cells visible. Nearly the whole of the posterior columns in the lumbo-sacral region may be destroyed, leaving only the cornu-commissural and oval areas of endogenous fibres. The vessels are often thickened in the sclerosed area, and not elsewhere; this change is secondary to the degeneration, and not causal. The walls of the arteries are often thickened, and there is hyaline degeneration of the media. Sometimes the vessels are so much thickened by this degenerative process as to become almost obliterated, especially when the sclerosis is advanced. The pia arachnoid membrane is also thickened, and often presents the appearances of chronic inflammation. By some authorities this meningeal thickening about the entrance of the posterior roots has been considered to have a causal relation to the atrophy of the fibres in the cord; but in early cases such meningitis is quite often not observed, and in cases where definite syphilitic meningitis is present the changes are never as symmetrical as in tabes. That tabes is a widespread primary degeneration, and not secondary to vascular changes in the posterior columns or meningitis, is strongly indicated in the frequent occurrence of primary optic atrophy, without any associated disease of the vessels supplying the retina. In early cases there may be no changes in the cells of the posterior root ganglia, but in advanced cases they usually present varying degrees of atrophy, chromatolysis, nuclear excentricity, and vacuolation. Similar changes are not infrequently found in the ciliary ganglion, and many observers associate these changes with the presence of the Argyll-Robertson pupil, which is otherwise accounted for by a hypothetical degeneration of fibres connecting the posterior colliculus with the third nerve nucleus (Meynert's fibres), since it is extremely rare to find changes in the cells of the third nerve nucleus itself.

In rare cases a progressive muscular atrophy, often of a true Arran-Duchenne type, is associated with slow atrophic changes and gradual disappearance of groups of anterior horn cells similar to those described in the chronic anterior poliomyelitis of progressive spinal muscular atrophy. Such atrophy is of too frequent occurrence to be regarded as a mere coincidence during the course of tabes, and is probably due to an acquired abiotrophy of the anterior horn cells, brought about by the prolonged action of the toxins which induce the other degenerative changes in tabes. Doubtless the cutting off of afferent impulses to the anterior horn

cells owing to the degeneration of the posterior root collaterals which arborize around cells at the base of the posterior root, the axons of which break up round the anterior horn cells, would act in an auxiliary manner in bringing about the anterior horn cell degeneration.

**Pathology.**—Some of the most important phenomena of tabes may be briefly explained by reference to Fig. 12 (p. 424). The afferent system of neurones conveys sensation from the skin, muscles, tendons, joints, etc., and these impulses travel by three sets of fibres: (1) Short collateral fibres, forming the spinal reflex arc; (2) medium-length fibres, which break up round the cells of Clarke's column, from which axis cylinders pass to form the direct cerebellar tracts, so forming the second or cerebellar arcs of the nervous system; (3) long fibres, which form Goll's column, and finally arborize around the cells of the nucleus gracilis, thence passing by the fillet to the thalamus, where they again relay on their way to the cerebral cortex, forming part of the highest or third arc of the central nervous system. There are thus three nervous circles—spinal reflex, cerebellar, and cerebral—all of which in tabes are more or less interrupted by the degeneration of the primary proto-neurones. The true motor neurones, through which impulses finally pass to control the muscles, are situated in the anterior horn. In the vast majority of cases of tabes, and indeed in all early cases, these are unaffected. Accordingly, muscular wasting is absent, and, similarly, there is no paralysis or great loss of muscular strength, but rather a loss of ability to properly apply that strength to the best advantage, owing to the deficient muscular tonus and the want of proper co-ordination, which are so characteristic of the disease. The loss of tonus, like that of the knee-jerk, is due both to the interruption of the spinal arc and to that of the cerebellar arcs occasioned by the degeneration of the anterior horn collaterals, and of the fibres which arborize around the cells of Clarke's column. By these degenerations the anterior horn cells are deprived of the afferent impulses, which in health they are constantly receiving and passing on to the muscles, to maintain normal tonus. In itself this loss of tonus largely accounts for the inco-ordination, which is proportional to a great extent to the hypotonus present.

**Inco-ordination.**—In order that equilibration, which is associated with the maintenance of the upright position and accurate poise of the body, may be unimpaired, and that there be no sign of inco-ordination of muscular movement, it is primarily necessary that the whole cerebellar mechanism, especially the afferent and efferent connections of the middle lobe, should be intact. Pressure impulses and impulses from muscles, tendons, bones, and joints, are constantly passing by means of the direct cerebellar tract to the middle lobe of the cerebellum. In health these sources furnish

accurate information to the cerebellum as to the exact position of the limbs in space, and other and most important supplies of afferent information concerning the position of the body in space reach the cerebellum from the semicircular canals by means of the vestibular nerve, and the muscle sense impressions from the ocular muscles by means of the posterior longitudinal bundle. In conditions of health all these impulses are in harmony, and there is no cerebellar confusion. Hence the functions of equilibration and of progression are largely involuntary, and are carried out for the most part without any great cerebral interference, and accordingly sense of vision is unnecessary. Now, in the case of tabes this fine cerebellar mechanism is interfered with in proportion to the degree of degeneration of the proto-neurones arborizing about the cells of Clarke's column. Similarly, in Friedreich's ataxia the extreme ataxia is associated with atrophy, and partial disappearance of Clarke's column of cells and the direct cerebellar tracts, while superficial sensation is normal. There may be in tabes every degree of loss of cerebellar function, from the mildest inco-ordination to a complete inability to maintain the upright position. In early cases, however, and as a result of education by proper exercises, visual impulses are largely made use of to replace the lack of muscle sense impressions, and to correct false impressions coming by way of degenerating neurones. Thus, a patient suffering from tabes will often walk during the daylight with a considerable degree of accuracy, while, on the contrary, the darkness causes him to stumble, and in advanced cases lose his power of maintaining the upright position. Hence the use of Romberg's sign in the diagnosis of tabes. As the disease progresses, walking, and, indeed, any voluntary movements of the affected parts, become more and more increasingly associated with voluntary attention, and any momentary lapsing of attention greatly increases the inco-ordination. This is due to the increasing degeneration in the posterior columns of the cord, which convey muscle-sense impressions (used in the broadest sense) to the cerebellum, which initiates all voluntary movements.

The fine cerebral adjustment of co-ordination is continually and successively, by new combinations, infinite in number and variety, regulating the innervation currents of an infinite variety of spinal neurones, and thus adjusting the delicate tensions of correlated groups of minute muscles engaged in the expression of our thoughts and emotions. In general paralysis, the morbid process, early in the disease, strikes this fine adjustment in the cerebral cortex. The system of association neurones, which co-ordinate and associate the kinæsthetic impressions of near and distant related ideation centres with the psycho-motor neurones, are in a state of progressive decay, and although there may be no disease of the efferent path from the cortex in the early stage of the disease, yet, owing to defective and unequable stimulation of the cortical

psycho-motor neurones, there is a failure in the precision of the reciprocal innervation of correlated groups of muscles used in verbal and written speech, manifest by tremor and inco-ordination. Some cases show this very markedly, without proportional dementia and delusions. We must suppose that these are examples of functional selection in the morbid process.

The lightning pains may be explained by the degeneration of the root fibres, and their paroxysmal character is probably due to exacerbations of the degenerative process, since the objective physical signs are often increased after a severe attack. The partial anæsthesia, which is so constant a sign, may be accounted for by the partial degeneration of the roots. Sherrington has shown that at least three roots overlap one another in a skin area, and in order to produce complete loss of sensation in a part all three roots must be divided. If there is pronounced analgesia or anæsthesia, the peripheral nerves are probably affected.

**General Paralysis.**—This disease has increased very considerably in later years, partly owing to the increased prevalence and dissemination of syphilis, owing to the tendency of the people to crowd into the cities, and increased means and cheapness of locomotion; partly owing to the increased exigencies and stress of modern life. As previously mentioned, the etiology of general paralysis and of tabes is really the same. Both tabes and general paralysis were at first regarded as the result of chronic interstitial, inflammatory changes, producing sclerosis, which led to a degeneration of the nervous elements; but both are now regarded as primary atrophic degenerations of the proper neural elements. In the former the afferent primary proto-neurones are affected, while in the latter the pyramidal cells of the cortex, with their axons, are largely the seat of degeneration. The inflammatory changes in the membranes around the vessels in general paralysis are in all probability secondary to the degeneration of the nervous elements.

**Morbid Anatomy.**—The dura mater is often found to be thickened and adherent to the skull-cap. On opening the dura, an excess of cerebrospinal fluid escapes, and there is obvious atrophy of the brain, especially of the frontal and central convolutions. If the patient has recently had seizures, a film of recent or old blood-clot may occasionally be observed, which may or may not be adherent to the dura mater. It may be partially organized, and some of the newly-formed vessels may have given way, giving rise to extravasation of fresh blood into the laminated membrane. However, this condition is comparatively rarely observed, now that the care of patients is so much improved, and they are prevented from injuring themselves by falls, etc. The pia arachnoid has a thickened, opalescent appearance, and the sulci are distended with fluid. The weight of the brain may be diminished by one-third in extreme cases. The hemispheres have proportionally lost

much more weight than the pons and cerebellum. The normal relationship of the weight of the cerebellum to that of the whole brain is one-eighth, while in cases of general paralysis it may be as high as one-sixth. The left hemisphere usually weighs less than the right. The thickening of the pia arachnoid membrane is most marked over the central and frontal convolutions, and likewise the atrophy of the convolutions is most marked over the same areas. It will be found, especially in these regions, that on stripping the membranes the brain substance tears away, leaving a characteristic worm-eaten appearance, not unlike that seen in granular kidney, and for the same reason. The grey matter of the cortex is diminished in thickness, and is of a dull pinkish-grey colour, owing to increased vascularity. The line of Gennari in the calcarine region, and the line of Baillarger in the grey matter of the central convolutions, are practically indistinguishable. One of the most characteristic macroscopical signs is the granular appearance of the ependyma of the lateral ventricles, and the even more marked granularity, giving a frosted appearance to the floor of the fourth ventricle. This granular appearance is probably evidence of irritative products due to neuronic decay and some latent toxin of syphilis which are present in the cerebrospinal fluid, and upon which the Wassermann reaction depends. In no other disease, except brain syphilis, is this change met with. The atrophy affects in the same way, but to a much smaller degree, the spinal cord, where the degenerations of tabes are not infrequently found to be present, combined with a varying degree of degeneration of the pyramidal tracts.

**Microscopical Examination.**—In sections of the cerebral cortex stained with polychrome eosin, it will be found that there is an obvious increase of vascularity of the grey matter. Vessel walls are changed, endothelial cells are swollen and proliferating; the perivascular space surrounding the vessels of the cortex, meninges, and to a lesser extent of the basal ganglia and brain stem, are found to be packed with proliferating cells of two kinds—lymphocytes and plasma cells—the latter being especially characteristic of brain syphilis and general paralysis. The presence of rod cells (Stäbchenzellen) have been noted by Alzheimer. Neuroglia cells are greatly increased in number and size, long branching processes can be traced to the small bloodvessels, and there is a marked subpial felting of neuroglia fibres. In contrast to the normal five layers of neurones forming the columns of Meynert, in general paralysis many cells have undergone total destruction; others are altered in shape, processes broken off, the apical processes corkscrewed as the result of atrophy of the dendritic terminations, which serve to attach them to the surface. The apical processes thus become slack, and allow the cells to assume abnormal positions, so breaking up the columnar arrangement of the cortical neurones. Some cells are

swollen, while others are atrophied. Varying degrees of chromatolysis and excentricity of the nuclei are observed, while many of the cells have entirely disappeared. In sections stained by Cajal's method there is seen to be marked disintegration of the intracellular, neuro-fibrillary network. By the Marchi and Marchi-Pal methods it is observed that many of the association neuraxons are degenerated and are in various stages of destruction, while the tangential system of fibres is almost entirely absent. The effect of the lesions just described is a gradually progressive dementia, owing to the atrophy of the association neurones of the cortex. There is no doubt that in this disease the association neurones suffer earliest, most extensively, and most severely. The higher association systems, which have been developed later philogenetically and ontogenetically, are the supragranular pyramids, and it is this layer which is the first to suffer, and suffers most severely, from the prolonged action of the toxins which induce the disease. In later stages, however, the other nervous elements become involved, and the Betz cells of the central convolutions are seen to be in various stages of disintegration. Hence the degeneration observed in the pyramidal tracts.

## WORKS TO BE CONSULTED.

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## CHAPTER XI

# RESPIRATION

By J. S. HALDANE

Under the heading of Respiration we may conveniently group together all the bodily processes concerned in the conveyance of oxygen from the external air to the living tissues, and of carbon dioxide from the living tissues to the air. Hence, respiration includes the act of breathing, the exchange of oxygen and carbon dioxide between the air of the lung alveoli and the blood, the conveyance of these gases by the blood, and their exchange between the blood and the tissues. One or more of any of these processes may be interfered with under abnormal or pathological conditions.

To understand how pathological conditions interfere with respiration it is essential to have a clear conception of normal respiration and the manner in which it is regulated, and a short account of this subject will first be given.

## I. NORMAL RESPIRATION.

**Regulation of Breathing.**—The movements of breathing are innervated from a nervous centre situated in the medulla oblongata, in the grey substance of the floor of the fourth ventricle a little above the point of the calamus scriptorius. The part above this may be sliced away without stopping the respiratory movements, but they completely cease when the part indicated is destroyed. The movements continue after all afferent nervous paths or connections with higher centres have been severed, and they are undoubtedly dependent in the main on the condition of the blood passing through the centre.

The key to the main conditions governing the movements of breathing has been furnished by examination of the air from the lung alveoli in man.* A sample of alveolar air is easily obtained by suddenly expiring deeply through a piece of wide-bored rubber tubing about 4 feet long. At the end of the expiration the sample is taken from the end of the tube nearest the mouth, and consists of pure alveolar air unmixed with the more or less pure air with which the respiratory passages are filled at the beginning of an

* Haldane and Priestley, *Journ. of Physiol.*, xxxii. 225, 1905.

expiration. By examining the alveolar air during normal breathing it is found that the breathing is so regulated as to keep the percentage of carbon dioxide practically constant for each individual, provided the barometric pressure is constant. For different men the normal percentage varies from about 4·7 to 6·4 per cent.—average about 5·6 per cent.—while in women and children the average is about 0·5 per cent. lower.* If air containing, say, 2 or 3 per cent. of carbon dioxide is breathed, the breathing immediately becomes deeper, so that the percentage in the alveolar air is only very slightly increased. An increase of as little as 0·25 per cent. in the alveolar air corresponds to an increase of as much as 100 per cent. in the depth of breathing. This shows how extraordinarily delicate is the reaction of the respiratory centre to the stimulus of carbon dioxide. A rise of 1 per cent. of carbon dioxide in the alveolar air causes marked air-hunger and great hyperpnœa.

From numerous experiments, there can be no doubt that the stimulus is conveyed to the centre by the blood. The nerve cells of the centre, or perhaps more probably specific end organs belonging to these cells, possibly at synapses, seem to possess a specific sensibility for the slightest increase or diminution of carbon dioxide, just as the end organs of the retina have a specific sensibility for light-waves.

Experiments made at different barometric pressures show that it is the partial pressure, and not the mere percentage, of carbon dioxide in the alveolar air which is the determining factor. If the barometric pressure is increased, the percentage falls in exact inverse proportion. All subsequent investigation has completely confirmed the conclusion originally reached by Paul Bert,† that the physiological effects of a gas vary with its partial pressure.

By forced breathing the proportion of carbon dioxide in the alveolar air, and consequently also in the arterial blood, may be reduced greatly. When this is so, the rhythmic activity of the respiratory centre is entirely suspended, so that a condition of apnœa is produced. Apnœa was formerly attributed to excess of oxygen in the arterial blood, and more recently to a summation of inhibitory stimuli conveyed by the vagus nerve. Neither of these causes has any influence in producing apnœa. Excess of oxygen in the air breathed has no influence at all on breathing under normal conditions, but if the rate or frequency of breathing oxygen is voluntarily or artificially increased, complete or partial apnœa of course follows from the accompanying removal of carbon dioxide. Vagus influence is excluded by the fact that excessive ventilation of the lungs does not produce apnœa if the percentage of the $CO_2$ in the alveolar air is prevented from falling; and from the teleological standpoint the inherent improbability of the existence of

* FitzGerald and Haldane, *Journ. of Physiol.*, xxxii. 486, 1905.

† *La Pression Barométrique*, 1878.

such a thing as "vagus apnœa" is very evident. Apnœa can be promptly produced in the ordinary way after the vagus nerves are cut, or in an animal whose respiratory centre is supplied with arterial blood from another animal in which the breathing is excessive.

In some persons and animals forced breathing causes no apnœa. This is probably due to the fact that the deficiency of carbon dioxide in the blood causes a compensatory constriction of the arterioles supplying the respiratory centre, the consequence being that the pressure of carbon dioxide in the centre is still sufficient, when deficiency of oxygen is superadded, to maintain rhythmic excitation.*

Any variations in the production of carbon dioxide within the body are met by corresponding variations in the ventilation of the lung alveoli, so that the partial pressure of carbon dioxide in the alveolar air, and consequently in the arterial blood, remains nearly constant. During muscular work, for instance, both production of carbon dioxide and alveolar ventilation may be increased to about ten times the normal. As absorption of oxygen by the lungs nearly always runs closely parallel with discharge of carbon dioxide, it is evident that this regulation of breathing insures a proper supply of oxygen as well as a proper discharge of carbon dioxide.

Within pretty wide limits, variations in the lung ventilation are usually brought about by varying the *depth* rather than the frequency of breathing. Frequency of breathing is thus no measure of the amount of air breathed, and varies greatly in different individuals during rest in a normal condition. Owing to the existence of the "dead space" of the respiratory air-passages, only about two-thirds of the pure air of an ordinary breath reach the lung alveoli. It is clear, therefore, that increased depth is more efficient than increased frequency of breathing. Indeed, very frequent, but at the same time shallow, breathing might coincide with quite insufficient ventilation of the alveoli.

It was discovered by Hering and Breuer that distension of the lungs inhibits inspiration, while collapse of the lungs stimulates inspiration, and that the effects are due to afferent impulses passing up the vagus nerve, and are absent if the vagi are severed. These observations have led to some erroneous theories as to the regulation of respiration. Their true interpretation is, that just as muscular movements are guided by afferent impulses, which inform us as to the completion or otherwise of the movements willed, so the action of the respiratory centre is guided by impulses which coordinate its action according to the degree of distension or collapse of the lungs.† Waste of time and muscular effort is thus saved in breathing, through the existence of the vagus impulses, but the

* Boothby, *Journ. of Physiol.*, lv. 328, 1912.

† Haldane, *Brit. Med. Journ.*, ii. 578, 1908; Scott, *Journ. of Physiol.*, xxxvii. 301, 1908.

stimulus which determines rhythmic respiratory activity under normal conditions is carbon dioxide alone.

Under abnormal or unusual conditions, other causes besides excess of carbon dioxide may help to excite the respiratory centre. When, for instance, air containing a very low percentage of oxygen is breathed, great hyperpnœa is usually produced. This is accompanied by marked cyanosis, indicating that the arterial blood is very imperfectly saturated with oxygen. In man the effect of want of oxygen is scarcely noticeable, as a rule, until the oxygen percentage of the inspired air falls below 14 per cent.; and the hyperpnœa only becomes very marked with a much lower percentage. The effect varies, however, according to circumstances, and varies very distinctly in different individuals under the same circumstances. Some persons, indeed, seem to lose consciousness without any preceding noticeable hyperpnœa, when breathing air in which the oxygen is rapidly diminishing; while others react with great hyperpnœa. The hyperpnœa is far more marked if the diminution in the oxygen is pretty rapid. With a slow diminution there seems to be very little hyperpnœa—none that would be readily noticed—before consciousness is lost.

Experiment shows that the effect of want of oxygen on the breathing depends very closely on the percentage (or rather partial pressure) of carbon dioxide in the alveolar air.* When the deficiency of oxygen occurs pretty rapidly, the percentage of carbon dioxide in the alveolar air remains fairly high, owing to the fact that it takes some time to diminish appreciably the large store of preformed carbon dioxide in the blood and tissues. If, on the other hand, the deficiency of oxygen occurs less rapidly, there is time for the slightly increased breathing to wash out the preformed carbon dioxide quietly, so that no marked hyperpnœa occurs. Cyanosis and loss of consciousness thus occur without any preceding struggle for breath. If a large amount of carbon dioxide has been first removed by voluntary forced breathing, or artificial breathing, extreme cyanosis, and even death in the case of animals subjected to prolonged and excessive artificial breathing,† occurs before any return of natural breathing. It is quite clear, therefore, that want of oxygen by itself does not excite the respiratory centre. It only lowers the threshold at which carbon dioxide excites the centre. Very considerable cyanosis may thus coexist with breathing which is only slightly deeper than usual. This increased depth of breathing may not be at all noticeable, and can only be demonstrated by analyzing the alveolar air and finding the partial pressure of carbon dioxide abnormally low. Such a condition exists in persons who are at considerable altitudes, and are thus suffering from anoxhæmia, and in various pathological conditions, as will be seen below.

* Haldane and Poulton, *Journ. of Physiol.*, xxxvii. 390, 1908.

† Yandell Henderson, *Amer. Journ. of Physiol.*, xxv. 310, 1910.

It is known that not only carbonic acid, but also other acids, have the power of exciting the respiratory centre. The deep breathing seen in cases of acid-poisoning or in diabetic coma, where the blood is charged with oxybutyric acid, is similar to the breathing produced by excess of carbonic acid. It is also known that want of oxygen in any form leads to the production in the living tissues of lactic acid, which passes into the blood, and may be abundantly present in the urine. All the respiratory phenomena produced by want of oxygen are consistent with the theory that it may not be want of oxygen itself, but the presence of diminished alkalinity of the blood or tissues of the respiratory centre, or of abnormal metabolic products, which accounts for the effect of want of oxygen in lowering the threshold at which carbonic acid excites the respiratory centre.* After fairly prolonged shortage of oxygen the threshold for carbon dioxide remains low for a considerable time after the oxygen want has been completely removed. The blood seems to take some time to regain its normal alkalinity.

The presence of lactic acid also explains a phenomenon which is observed after any severe muscular exertion, such as running a race or running quickly up several stairs. For about an hour after the exertion the alveolar carbon dioxide percentage remains quite distinctly low. During the severe exertion the oxygen-supply brought to the muscles by the circulation cannot keep pace with the consumption of oxygen, and consequently lactic acid is produced, and has been found in the blood and urine.† The alkalinity of the blood has also been found to be diminished, and the increase of lactic acid and diminished alkalinity last about the same time as the diminished alveolar carbon dioxide. The rapid diminution of the blood alkalinity during excessive exertion greatly increases the hyperpnœa, as a large amount of preformed carbon dioxide has to be washed out from the blood and tissues in order to compensate for the lowered exciting threshold of carbon dioxide partial pressure. For the same reason the respiratory quotient—*i.e.*, the relation of the volume of carbon dioxide given off to that of the oxygen absorbed by the body—is abnormally high. On settling down to continued hard work, the alkalinity of the blood ceases to diminish, unless the work is very excessive, and the excessive hyperpnœa passes off. This probably explains in part the well-known phenomenon of "second wind," and the desirability of taking hard work easily at first. Feldman and Hill‡ have found that when oxygen is breathed instead of air, the formation of lactic acid during muscular exertion is greatly diminished, as the supply of oxygen to the muscles is increased.

* Boycott and Haldane, *Journ. of Physiol.*, xxxvii. 355, 1908.

† Douglas and Haldane, *Journ. of Physiol.*, xxxviii. 420, 1909; Ryffel, *ibid.*, xxxix., p. xxix, 1909; Boycott and Chisolm, *Biochemical Journal*, v. 23, 1910.

‡ *Journ. of Physiol.*, xlii. 439, 1911.

Short exposure to want of oxygen acts as a rule so promptly on the respiratory centre, and the hyperpnœa disappears again so promptly when sufficient oxygen is supplied, that it seems almost certain that if it is lactic or other acid which acts on the centre it is formed, and perhaps again destroyed or assimilated, *in situ*.

The facts relating to the effects of carbon dioxide, and of acids and alkalies, on the respiratory centre suggest that it is to the hydrogen ion concentration that the centre really responds; but this supposition has not yet been experimentally verified.

In animals, such as dogs, which regulate their discharge of heat by increasing the frequency of breathing, rise of temperature excites the respiratory centre to very frequent and shallow respirations (polypnœa). In man the discharge of heat is regulated in other ways, and this type of breathing does not occur normally. With rise of body temperature produced artificially, however, there occurs a marked lowering of the threshold of alveolar carbon dioxide pressure in addition to an increase in the respiratory exchange. There is thus some hyperpnœa, which is markedly increased on any exertion. Whether this effect is directly caused by rise of temperature in the respiratory centre is not yet known.

In connection with pathological irregularities of breathing, it is a matter of considerable interest to understand why normal breathing follows so smoothly and easily the requirements of the body. At first sight it is not at all evident why the breathing is not irregular, the respiratory movements now overshooting the mark, and now entirely ceasing, as actually occurs in Cheyne-Stokes breathing. As we have just seen, the respiratory centre is sensitive to the minutest changes in the partial pressure of carbon dioxide in the blood. We might therefore expect it to start into violent activity on any sudden increase of production of carbon dioxide, as in muscular activity, and to be pulled up again rapidly and completely by the great fall in the carbon dioxide content of the arterial blood caused by the greatly increased pulmonary ventilation. The breathing would thus resemble the action of a steam-engine with a very sensitive governor and no flywheel. Breathing of this type is actually met with in disease and in healthy persons living at high altitudes, but under normal conditions it does not occur. For instance, the hyperpnœa accompanying muscular exertion comes on and passes off quite smoothly and regularly.

There is more than one reason for this. In the first place, the lungs contain a considerable amount of air (the so-called "reserve" and "residual" air), equivalent in volume to about six ordinary breaths. It thus takes some little time for this air to be greatly changed in composition, either by changes in the venosity of the venous blood or by changes in the rate of the pulmonary ventilation. Were it not for this considerable volume of air in the lungs, there would be risk of sudden fainting from lack of oxygen. In a

very small mammal a given volume of lung does ten or fifteen times as much work as the same volume of human lung, and we might therefore imagine the human lungs reduced to a tenth of their actual size, and yet efficiently performing their work of aerating the blood. The amount of air in the lungs would be so small, however, that any sudden demand for oxygen would produce an asphyxial condition of the blood before the respiratory centre responded.

A second and equally important reason of the smooth working of the respiratory centre is that the centre reacts somewhat slowly to changes in the partial pressure of carbon dioxide in the blood. This is probably due to the fact that, like other parts of the body, it has a considerable capacity for carbon dioxide, and thus takes some time to become saturated or desaturated with this gas to any given partial pressure. Even distilled water takes about thirty times as much carbon dioxide as it does of oxygen to saturate it to a given partial pressure. Thus the centre, though very sensitive to carbon dioxide, reacts slowly to it, and gradually catches up the proper amount of activity to compensate by increased ventilation of the lungs for increased production of $CO_2$ in the body. There is no need for hurry in this process, as the lungs contain plenty of oxygen to last over the preliminary period during which the adjustment is taking place.

In accordance with this explanation, it is found that if by forced breathing the carbon dioxide in the blood, and consequently in the respiratory centre, is reduced considerably so as to produce apnœa, the lungs being at the same time filled with oxygen to prevent want of oxygen cutting short the apnœa, natural breathing does not recommence until the percentage of carbon dioxide in the alveolar air has considerably exceeded the normal. And, conversely, if the breath is held, so as to increase the carbon dioxide pressure in the blood, and thus charge up the respiratory centre with an excess of this gas, the breathing is for some time much in excess of what is needed to reduce the alveolar carbon dioxide to normal.

We have seen above that under abnormal conditions the respiratory centre may be excited in consequence of want of oxygen aiding, directly or indirectly, the action of the carbon dioxide already present. Now, the tissues of the body have, practically speaking, no capacity for storing oxygen, and consequently we might expect that the respiratory centre would react very abruptly and excessively when directly exposed to want of oxygen. Such is actually the case, and the breathing tends to become periodic or irregular, in contrast to the smooth working of normal breathing. This irregular and very uncomfortable form of breathing is apt to occur if the partial pressure of oxygen in the inspired air is low, as at high altitudes. It is often specially distressing at night, sleep being disturbed by the person constantly being

FIG. 13.—FORCED BREATHING OF AIR FOR TWO MINUTES, FOLLOWED BY APNŒA FOR TWO MINUTES AND PERIODIC BREATHING FOR ABOUT FIVE MINUTES.

At *A*, Sample of alveolar air, $O_2$=11·44 %, $CO_2$=5·58 %. Second sample at *B*, $O_2$=13·55 %, $CO_2$=5·57 %. Time marks=5 seconds.

roused by a sudden feeling of impending suffocation; and on observation it will be found that deep breaths, accompanied by great air-hunger, are constantly being succeeded and preceded by shallow breaths or total cessation of breathing for a few seconds. The breathing is, in fact, like the action of an engine with a sensitive governor but no flywheel, and thus often becomes regularly periodic, as in typical Cheyne-Stokes breathing, which may be compared to "hunting" of the governor of a steam-engine or water-turbine.

This condition may easily be studied experimentally in normal persons at ordinary barometric pressure.* One very instructive method of producing temporary Cheyne-Stokes breathing is the following: An apnœa of about two minutes' duration is produced by forced breathing for about two or three minutes. At the end of the apnœa it is found (in many persons, at least) that, if the breathing is entirely left to itself, it becomes periodic, and remains so for some minutes, the periodicity gradually dying away, as shown in Fig. 13.

If the lungs be filled with oxygen instead of air at the end of the forced breathing, the apnœa is greatly prolonged, and the breathing recommences quite gently and regularly, without any sign of periodicity. It is thus want of oxygen which cuts short the apnœa, and at the same time gives rise to the Cheyne-Stokes breathing.

* Douglas and Haldane, *Journ. of Physiol.*, xxxviii. 401, 1909.

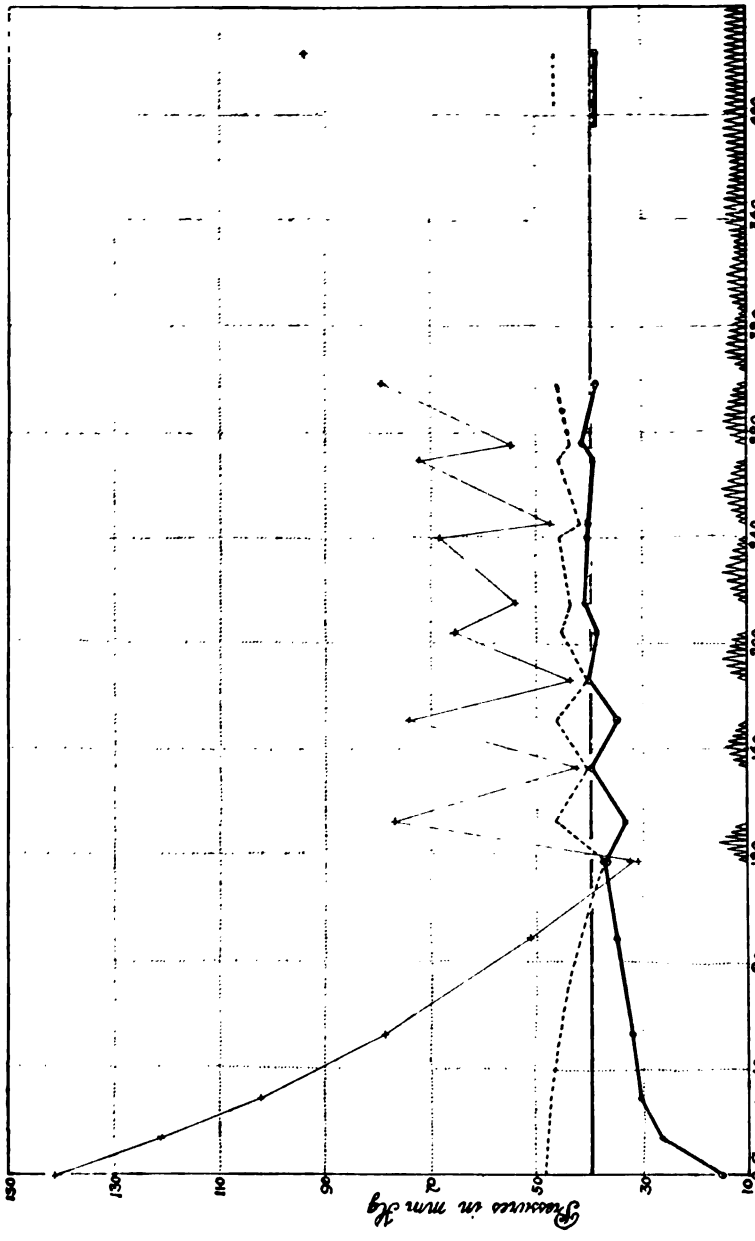



FIG. 14.—VARIATIONS IN ALVEOLAR GAS-PRESSURES AFTER FORCED BREATHING FOR TWO MINUTES.

Thin line = oxygen pressure; thick line = $CO_2$ pressure; double line = normal alveolar $CO_2$ pressure. The actual breathing is indicated at the lower part of the figure. The dotted line refers to experiments not dealt with in the text.

Fig. 14 shows the variation of oxygen and carbon dioxide pressure in the alveolar air during apnœa and subsequent periods of Cheyne-Stokes breathing. It will be noticed that after the first half-minute (which is occupied in bringing the alveolar carbon dioxide into gaseous equilibrium with the carbon dioxide of the blood) the alveolar carbon dioxide pressure rises very slowly, owing to the great storage capacity of the body for carbon dioxide, and consequent very slow rise in the carbon dioxide pressure of the venous blood. On the other hand, the alveolar oxygen falls very rapidly and evenly, the body having no storage reserve of oxygen except that in the alveolar air. The point at which oxygen want begins to tell on the respiratory centre is thus reached very suddenly, and the respiratory centre responds sharply, great air-hunger being at the same time experienced. The breathing at once raises the alveolar oxygen considerably, but does not much lower the alveolar carbon dioxide, since more of the latter gas is at once poured out from the reserve in the blood. The oxygen supply rapidly suffices to quiet the quickly responding respiratory centre, and apnœa again results, as the centre contains insufficient carbon dioxide for this gas to excite by itself. The alveolar oxygen again falls rapidly, and the whole process is repeated again and again until sufficient carbon dioxide has accumulated in the body to produce regular respiration in the normal manner.

When oxygen want is entirely eliminated the alveolar carbon dioxide rises well above the normal before respiration begins. The explanation of this phenomenon has already been given above. The excess of oxygen above the normal supply has no influence in counteracting the effect of carbon dioxide. The delay is due simply to the fact that rise in the carbon dioxide pressure of the centre lags behind that of the alveolar air. A very short further interval suffices to establish the normal correspondence, although oxygen is still breathed. The substitution of oxygen for air has no effect at all on the breathing unless abnormal want of oxygen exists, whether caused by deficiency of oxygen in the alveolar air, deficient circulation, deficient oxygen-carrying power of the blood, or deficient passage of oxygen from the alveolar air into the blood. Any of these causes may, of course, operate under various pathological conditions which will be considered later; and considerable stress has been laid at this point on the effects of oxygen want on the respiratory centre, as the matter is of great importance in the correct interpretation of respiratory symptoms in disease and the application of treatment. Oxygen want is also practically always the immediate cause of death in man.

**Conveyance of Oxygen and Carbon Dioxide by the Blood.**—Both oxygen and carbon dioxide are conveyed in the blood in the form of easily dissociable chemical compounds. The conveyance of

oxygen is of special interest, as it is liable to be interfered with in various ways under abnormal or pathological conditions.

As will be seen below, the blood becomes saturated with oxygen in the lungs at a partial pressure of about 13 per cent. of an atmosphere during rest, if the air breathed is normal. At this partial pressure it can only take up 0·3 c.c. of oxygen in simple solution per 100 c.c. of blood, whereas it yields to a vacuum more than fifty times as much oxygen, so that nearly all the oxygen is in chemical combination. As is well known, it is found to be combined with the hæmoglobin of the red corpuscles, forming a scarlet-coloured compound which contrasts with the dark blue of hæmoglobin.

The gases contained in the blood can be measured with the help of the vacuum pump. A much more convenient method for the oxygen and carbon dioxide is based on the fact that ferricyanide liberates the oxygen of oxyhæmoglobin, and an acid liberates the combined carbon dioxide.* A still simpler and extremely accurate apparatus for determining the oxygen-carrying power of blood is the hæmoglobinometer of Gowers and the writer. The oxygen-carrying power of blood varies directly with its colouring power, except in the very exceptional cases where an abnormal pigment is present in large quantities in the blood. This is true, not only of the blood of different mammals, but also of the blood in cases of anæmia, polycythæmia, heart disease, and other abnormal conditions. Hence the Gowers-Haldane hæmoglobinometer, which is standardized to blood of a definite normal oxygen capacity, gives the oxygen-carrying power of the blood. Results obtained with the spectrophotometer and other elaborate instruments are often of very doubtful value, for reasons which need hardly be detailed here. In human blood the hæmoglobin has an average oxygen capacity of 18·5 c.c. per 100 c.c. of blood, and this corresponds to 100 per cent. on the hæmoglobinometer scale.

The oxyhæmoglobin of blood has the property of becoming dissociated into free oxygen and hæmoglobin in proportion as the partial pressure of the oxygen in the surrounding medium is reduced. The laws of this dissociation, and the conditions under which it occurs, have been worked out during the last few years, mainly by Bohr, Barcroft, and their respective pupils. It has been shown, in the first place, that the oxyhæmoglobin present in the red corpuscles dissociates much more easily than oxyhæmoglobin in simple aqueous solution and according to a different law. This fact led Bohr to conclude, erroneously, that the oxyhæmoglobin of the corpuscles is a different compound. Fig. 15 represents graphically the degrees of dissociation of the oxyhæmoglobin of fresh blood from two men and from mice at varying partial pressures of oxygen.

It will be noticed that the dissociation curve has a very peculiar form. At any given partial pressure of oxygen the proportion of

* Barcroft and Haldane, *Journ. of Physiol.*, xxviii. 232, 1902.

oxyhæmoglobin to hæmoglobin is not, as was formerly assumed, proportional to the partial pressure of the oxygen. At the middle part of the curve, which is the physiologically important part, the dissociation proceeds at a far more rapid rate. This fact is evidently of great physiological advantage, as it renders the supply of oxygen in the oxyhæmoglobin much more available than it otherwise would be; for a comparatively small fall of partial pressure in the blood

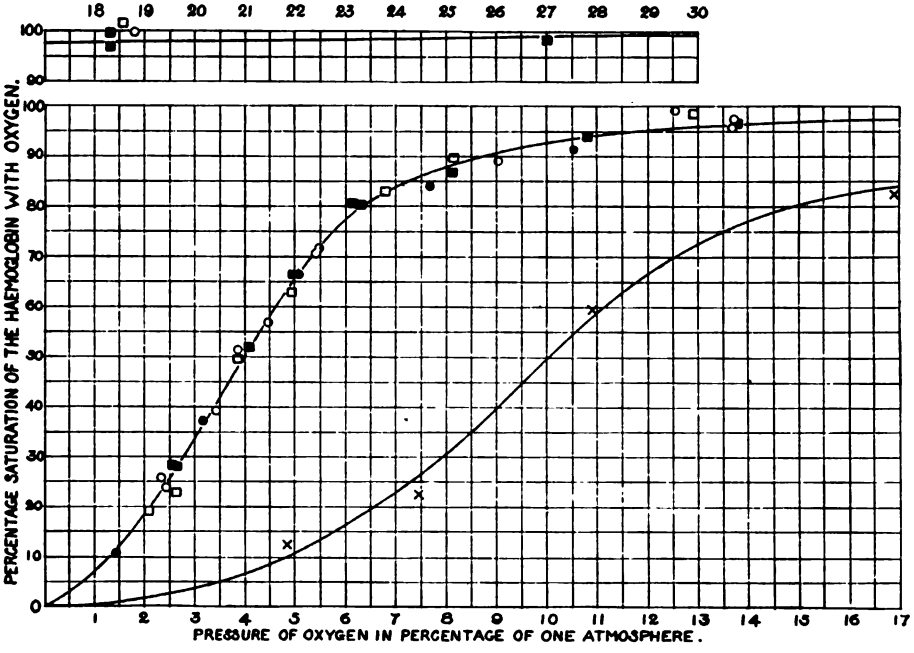



FIG. 15.—DISSOCIATION CURVES OF OXYHÆMOGLOBIN IN PRESENCE OF 40 MM. PRESSURE OF $CO_2$ AT 38°.

| | | | | | |
|---|---|---|---|---|---|
| ○ | Blood of C. G. D., using ammonia in blood-gas apparatus. | | | | |
| ● | ,, | ,, | ,, | $Na_2CO_3$ | ,, ,, |
| □ | ,, | J. S. H., | ,, | ammonia | ,, ,, |
| ■ | ,, | ,, | ,, | $Na_2CO_3$ | ,, ,, |
| × | Mixed blood of six mice, using ammonia | | | | ,, ,, |

as it passes through the capillaries leads to a great liberation of oxygen. It has recently been shown by Barcroft and Roberts* that the peculiarity of the form of the curve depends in some way on the salts of the blood. Dialyzed blood gives a curve following the simple law of mass action already alluded to. The somewhat different curves given by the blood of different animals, and even different individuals of the same species, appear to depend also on constituents which are removable by dialysis. The dissociation

* *Journ. of Physiol.*, xxxix. 143, 1909.

curves of human and dogs' blood differ considerably, but human hæmoglobin gives the curve of dogs' blood when dissolved in water containing the salts of dogs' blood in their proper proportion.

Another point of physiological interest is that, as discovered by Bohr and his collaborators, the dissociation of oxyhæmoglobin is aided by the presence of carbon dioxide.* Thus, the increase of carbon dioxide in the blood passing through the capillaries helps to liberate oxygen from the hæmoglobin, while the diminution of carbon dioxide as the blood passes through the lungs must aid the taking up of oxygen by the blood. In the absence of carbon dioxide the general form of the curve shown in Fig. 3 remains the same, but the curve is shifted to the left, so that for any given percentage dissociation the partial pressure of oxygen must be reduced by about half. Not only carbonic acid, but also other acids shift the curve to the right; hence the formation of lactic acid in an active muscle helps the oxygen supply to it, as Barcroft has shown.

Another factor which helps to liberate oxygen from oxyhæmoglobin is rise of temperature. In actively working muscles, etc., the temperature must rise very appreciably higher than in the mixed venous blood which reaches the heart, and contains all the comparatively cool blood returning from the skin. This slight rise of temperature affects very considerably the dissociation curve of oxyhæmoglobin in the direction of facilitating the giving off of oxygen, as Barcroft and King have shown.†

In consequence of these various causes the curve of dissociation in the living body, as the blood passes through the capillaries, is steeper, and has a more marked double bend than Fig. 15.‡

We can now form a clear idea of the manner in which oxygen is conveyed to the capillaries. The hæmoglobin of venous blood takes up oxygen in the lungs in consequence of the rise of partial pressure of oxygen in the plasma, due to the stream of oxygen molecules passing from the alveolar air through the lung epithelium and capillary walls into the blood. The hæmoglobin thus becomes nearly saturated with oxygen under conditions which will be discussed more fully below. The process is aided by discharge of carbon dioxide from the blood, and by the lower temperature of the venous blood than exists in the capillaries at many points. The blood is now carried by the circulation to the capillaries, where the partial pressure of oxygen is rapidly lowered by the passage of oxygen molecules outwards towards the tissues, in which the oxygen finally disappears as such. In consequence of the lowering of the oxygen pressure in the plasma, the oxyhæmoglobin of the corpuscles is dissociated to a greater or less extent, the process being

* Bohr, Hasselbalch, and Krogh, *Skand. Archiv f. Physiol.*, xvi. 402, 1904.

† *Journ. of Physiol.*, xxxix. 374, 1909.

‡ For a discussion of the mode of action of salts, etc., on the dissociation curve, see Douglas, Haldane, and J. B. S. Haldane, *Journ. of Physiol.*, xliv. 275, 1912.

aided by the accompanying rise of partial pressure of carbon dioxide and rise of temperature should this occur. On account of the influence of the salts of the blood, the oxyhæmoglobin can give up nearly all its oxygen without a very excessive fall in the oxygen pressure. It is very possible that the capillary endothelium regulates to a large extent the stream of oxygen from the blood to the tissues, and of carbon dioxide outwards to the blood. On this point we possess as yet no information, but in view of what is already known as to the physiological properties of this endothelium it is rash to assume, as is usually done, that the process is one of unregulated diffusion.

The extent to which the oxygen of the red corpuscles is used up in the tissues seems to vary greatly in different parts of the body and different conditions of functional activity, and we know little as yet as to the extent to which using up of this oxygen is consistent with a sufficient supply of oxygen to the tissues. The cerebrum is, however, specially sensitive to any diminution of the partial pressure of oxygen in its capillaries, and the venous blood from the brain seems to contain normally a good deal more oxygen than the blood from most other parts.

By artificially raising the partial pressure of oxygen in the arterial blood we can so increase the amount of oxygen which is in simple solution that the body can dispense for the time with the oxygen-carrying power of the hæmoglobin. Thus, when an animal is in oxygen at a pressure of two atmospheres, it continues to live and move about almost as usual after the whole of its hæmoglobin has been completely thrown out of action by carbon monoxide or by a poison (such as a nitrite) which converts oxyhæmoglobin into methæmoglobin. Normally, as we have seen, the arterial blood only contains about 0·3 per cent. by volume of oxygen. At two atmospheres pressure of oxygen this quantity is increased to nearly 5 per cent., the whole of which is very readily available. Even at normal atmospheric pressure the supply of dissolved oxygen in the arterial blood becomes very considerable when pure oxygen is breathed, and will suffice to tide the body over various emergencies.

The process of conveyance of carbon dioxide from the tissues to the lungs is very similar to that of the conveyance of oxygen. Carbon dioxide is, however, far more soluble in water or in the blood than oxygen is, so that even if the blood contained nothing capable of combining chemically with carbon dioxide, and dissociating freely, it might still be capable of carrying sufficient carbon dioxide to keep the body alive. Arterial blood in man is probably saturated with carbon dioxide in the lungs at a partial pressure of about 5·3 per cent. of an atmosphere. At this pressure it contains about 2·6 per cent. by volume of carbon dioxide in simple solution, and about 40 per cent. in all. The mixed venous blood contains about 5 per cent. more of carbon dioxide—about

45 per cent. in all—only about a tenth of the extra carbon dioxide in the venous blood being in free solution. An increased rate of circulation, combined with a moderately increased rise in the partial pressure of the gas in the venous blood, would, however, enable the body to dispense wholly with the chemical compounds concerned normally in the conveyance of carbon dioxide, and some approximation to this condition is known to occur in acid-poisoning.

Most of the carbon dioxide in blood appears to be present in the form of bicarbonate of soda or potash. Proteins, including hæmoglobin, and possibly other substances in the blood, act as weak acids, and so render the bicarbonates very easily dissociable. There is also evidence, however, that hæmoglobin by itself forms an easily dissociable compound with carbon dioxide, independently of the presence of loosely combined oxygen to form oxyhæmoglobin. In any case, the dissociable compounds are of such a nature that a rise of 1 or 2 per cent. of an atmosphere in the partial pressure of carbon dioxide enables the blood to take up the normal amount of carbon dioxide carried from the tissues to the lungs. In this way the partial pressure of carbon dioxide in the tissues is kept within very narrow limits, going neither too high nor too low. The body appears to be very sensitive to variations in one direction or the other. The central nervous system, apart from the respiratory centre, is specially sensitive, headache and loss of consciousness being easily produced by unusual excess of carbon dioxide. The effects, direct or indirect, of too little carbon dioxide are also well marked. Forced breathing, for instance, causes a number of very unpleasant symptoms, which are quite absent in equally hyperpnœic breathing produced by natural stimuli.

The due removal of carbon dioxide is thus a very important function of the blood, although the supply of oxygen is a matter of far greater urgency.

**The Gaseous Exchange between the Alveolar Air of the Lungs and the Blood.**—The process by which oxygen penetrates inwards, and carbon dioxide outwards, through the very thin septum of living tissue separating the blood and the air in the lung alveoli is of much interest both to physiologists and pathologists. Any interference with this process in disease is evidently of great importance.

Calculations have been made to show that the exchange of gases must occur by diffusion alone with the utmost ease, and would, thus, not readily be interfered with by pathological processes. The basis of these calculations is, however, almost worthless. It has recently been pointed out by Bohr,* however, that we can measure the rate of diffusion through the septum, with a known difference of gaseous pressure on the two sides of it, in the case of carbon

* *Skand. Archiv f. Physiol.*, xxii. 221, 1909; *Centralbl. f. Physiologie*, xxiii., p. 374, 1909; also A. and M. Krogh, *Skand. Arch. f. Physiol.*, xxiii. 236, 1910.

monoxide, which, as will be shown below, is a physiologically indifferent gas which may be expected to diffuse freely through the body in every direction. If air containing a given (and not too high) percentage of carbon monoxide is breathed for a short time, part of it passes into the blood, where it at once combines with hæmoglobin, so that its partial pressure is reduced to practically nothing, while part escapes absorption, and is expired. Actually about half the gas breathed escapes absorption. It is easy to determine the average percentage or partial pressure of the gas in the alveolar air, and the average rate of its absorption under the existing conditions. From this we can calculate the rate at which oxygen or carbon dioxide would pass through the septum, with the actual differences of partial pressure which prevail under physiological conditions. In this calculation we must make allowance for the greater solubility of oxygen, and far greater solubility of carbon dioxide; also for the fact that in each alveolar capillary the difference of partial pressure on the two sides of the septum must be diminishing from the venous to the arterial end. Bohr's calculation shows that, while all the carbon dioxide actually eliminated may pass through by diffusion, the quantity of oxygen required during considerable muscular exertion can barely do so. But as this quantity of oxygen certainly does pass through, and the arterial blood during muscular exertions seems to be very fully saturated with oxygen, we must conclude that other factors besides diffusion are probably in play.

The question has also been attacked by several physiologists in a more direct manner.* By means of the apparatus known as the "aerotonometer" the partial pressure of oxygen and carbon dioxide in the arterial or venous blood has been estimated and compared with those in the alveolar air. In the most recent form given to it by Krogh, the aerotonometer consists of a piece of narrow-bored graduated glass tube, with a chamber blown at each of its ends. The upper chamber is filled with salt solution, while the blood from the animal is allowed to flow in a jet through the second chamber, which was at first also filled with salt solution. The graduated part of the tube at first contains a column of air. This is displaced downwards into the lower chamber by means of a screw piston in the upper chamber, and the bubble of air thus projected into the lower chamber is exposed to the jet of blood. The gas pressures in the bubble and in the blood quickly equalize themselves, and the bubble is then withdrawn into the upper tube and measured. The blood is now displaced by caustic soda, and the air exposed to this and remeasured, so as to determine the percentage of carbon dioxide. In a similar way the oxygen percentage is measured. When all the necessary precautions are taken, the

* An account of the discussion up to 1905 is given by Bohr, Nagel's *Handbuch der Physiol.*, vol. i., 1905.

partial pressures of oxygen and carbon dioxide in the blood can be calculated.

In the great majority of experiments with aerotonometers, the partial pressure of oxygen in the blood has been found to be distinctly below that in the alveolar air, while the carbon dioxide pressures are about equal.* This result appears to confirm the theory that the exchange is by mere diffusion. In some of Bohr's experiments, however, the results were inconsistent with the diffusion theory, as they indicated a higher pressure of oxygen in the blood than in the alveolar air, and a lower pressure of carbon dioxide.†

Lorrain Smith and the writer, using a quite different method, which will be explained below in connection with carbon monoxide poisoning, also obtained results adverse to the diffusion theory. These experiments have been quite recently checked and tested very carefully by Douglas and the writer, who have come to the conclusion that, in the animals and men experimented on, diffusion alone will explain the process during rest, and when want of oxygen is not present, but that whenever there is want of oxygen a process of active absorption by the lung epithelium, or the endothelium of the lung capillaries, comes into play.‡ In carbonic oxide poisoning, for instance, where there is great want of oxygen, the oxygen pressure in the arterial blood is raised very considerably above that in the alveolar air or external air. In muscular work also there is active absorption, so that active absorption is an every-day occurrence. As will be shown below, active absorption is constantly present after acclimatization to high altitudes. These conclusions seem to be in harmony with all the results hitherto obtained, and to be physiologically probable. It is only where active absorption of oxygen or excretion of carbon dioxide would be of use to the body, as under conditions where diffusion would not suffice, that we should expect to find active absorption or excretion.

It is evident that anything interfering with the healthiness of the lung tissues would impair their power of active absorption and excretion. Apart from this, however, anything causing thickening of any sort in the septum between alveolar air and blood, or any exudation or œdema, would seriously hinder diffusion, since, as already shown, diffusion alone does little more than suffice for ordinary resting requirements. Lorrain Smith found that, after an incipient pneumonic condition had been produced in the lungs by exposing animals for some time to oxygen at high pressure, the oxygen pressure in the arterial blood when carbon monoxide was administered became far lower than in healthy animals; and this was so although hyperpnœa was present, which would tend to

* Krogh, *Skand. Archiv f. Physiol.*, xxiii. 179-278, 1910.
† *Centralbl. f. Physiol.*, xxi. 369, 1907.
‡ *Journ. of Physiol.*, xliv. 305, 1912.

raise the oxygen pressure in the alveolar air. These experiments, and other similar ones, indicate the importance of the condition of the lung epithelium in conditions of disease. At high altitudes this importance is still greater, since the alveolar oxygen pressure is much lower. Pneumonia seems to be much more fatal at high altitudes than near sea-level. The breathing of air with an increased percentage or pressure of oxygen might be of much use.

Active absorption or excretion of gas by the lungs is not an isolated phenomenon. We know that the swim-bladder, of which the epithelium is developed from the same embryonic layer as the lung epithelium, possesses in a marked degree the power of actively secreting oxygen. The oxygen within the swim-bladder may be secreted at a partial pressure at least 500 times as great as that in the surrounding sea-water in the case of deep-sea fishes.

Douglas and Haldane found that in man during rest the partial pressure of oxygen in the arterial blood is equal to that in the alveolar air (about 13 per cent. of an atmosphere, or 100 millimetres of mercury). At this oxygen pressure the hæmoglobin, as shown in Fig. 3, is 96 per cent. saturated. Hence average human arterial blood contains (since the hæmoglobin is capable of taking up 18·5 per cent.) $18{\cdot}5 \times \frac{96}{100} = 17{\cdot}76$ per cent. of oxygen in combination. There is also 0·36 per cent. in simple solution, so that 18·1 per cent. is present in all. If pure oxygen were breathed, the extra quantity of oxygen taken up would be about 2·1 per cent. in solution and 0·7 per cent. in combination—2·8 per cent. in all, or about a sixth more than when air is breathed.

We have seen above how the average composition of the alveolar air may be determined, and how important this average composition is. The question occurs, however, whether the composition of alveolar air is the same at all parts of the lung, and all the blood is equally aerated. It has often been supposed, for instance, that the aeration is normally less perfect at the apices of the lung.

If aeration were normally less complete at some parts than others, we should expect that some of the blood would be less completely saturated with oxygen than the rest. As a consequence, the partial pressure of oxygen in the mixed arterial blood would be markedly below that in the average alveolar air. This would follow from the form of the dissociation curve of oxyhæmoglobin. As a matter of fact it is not so during health. Everything suggests, therefore, that the aeration of all the lung alveoli is nearly the same.

If so, how is this brought about? Where a number of branching air-ducts exist, as in the lungs, there would seem to be much difficulty in obtaining a physiologically even distribution of air. The great difficulties and constant failures in systems of branching air-ducts for ventilation purposes are well known to architects and others. The problem seems specially complex in the lung, as the

alveolar air-supply must be suited to the alveolar blood-supply. The lung, however, possesses in the bronchial and arterial muscles a means by which the air and blood distribution may be exactly regulated, and it seems probable that they are actually used for this purpose, so that the distribution of air to all parts is properly regulated. That the bronchial muscles can act promptly and powerfully has been shown by exciting the vagus nerve, in which not only vaso-constrictor fibres, but also, as has been shown by Brodie and Dixon,* broncho-dilator fibres. Dixon has quite recently communicated to the Physiological Society experiments showing that excitation of the sympathetic causes great dilatation of the bronchi. We know nothing as yet of local conditions in the lung which determine the degree of constriction of various bronchi, but the existence of such local conditions, and their connection with the proper distribution of air, may be confidently predicted. The bronchial muscles are certainly not there as a means for producing asthma or for puzzling physiologists, and it is difficult to see what other function they can have than that of regulating the distribution of air, just as the muscles of the bloodvessels regulate the distribution of blood. Any serious failure of this regulation, whether from mechanical obstruction, as in bronchitis, or from disturbance of innervation, would not only lead to imperfect oxygenation of the blood, but to serious distortions of the lung substance and probable emphysema.

Douglas and Haldane† have recently shown that during the hyperpnœa of muscular exertion the capacity of the respiratory passages is increased to as much as four times the resting capacity. This is evidently due to dilatation of the bronchi. If the "dead space" due to the capacity of the respiratory passages were as great during rest as during work, hardly any of the air inspired in an average breath during rest could reach the lung alveoli; but during work the depth of each breath is so much increased that the increased dead space is of little account, while the resistance to inspiration and expiration is greatly diminished.

**Respiratory Regulation of the Circulation.**—Unless oxygen and carbon dioxide were conveyed to and from the tissues by the circulation, and unless the rate of blood-flow to and from the different parts of the body were regulated in such a way as to cover the respiratory requirements of each part, it is evident that regulation of the respiratory movements, and particularly the form of regulation which actually exists, would be of but limited use. The respiratory movements keep the arterial blood normal in composition, but under ordinary circumstances they do no more. They cannot materially increase the amount of oxygen in the arterial

* *Journ. of Physiol.*, xxix. 97, 1903; also *Trans. Path. Soc. of Lond.*, vol. liv., 1903.

† *Journ. of Physiol.*, xlv. 235, 1912.

blood; and as under resting conditions about half of the oxygen in the blood supplying the muscles appears to be used up, while an active muscle may require twenty or thirty times as much oxygen during activity as during rest, it is clear that the only way in which the muscle can be properly supplied with oxygen is by a great increase in the local circulation. This in turn involves an increase, greater or less according to the amount of work done, in the rate of blood-flow through the heart and lungs.

It must be remembered that as regards oxygen-supply the body leads a hand-to-mouth existence. It carries about stores, which are constantly being drawn on or replenished, of food material, water, and salts, but practically no store of oxygen except the small quantity in the alveolar air and the blood; and any cutting off of the oxygen-supply is fatal within very few minutes, as the heart stops and the central nervous system is injured beyond recovery.

It is well known that, as a general rule, increased activity of any organ is accompanied or rapidly followed by increase in the flow of blood through it. This may be brought about either through the agency of the central nervous system and vasomotor nerves, or by a more direct local action of the products of metabolism. The physiological necessity of this increased flow is evident, as oxygen and other substances must be supplied to the organ in increased amount, while carbon dioxide and other products of metabolism must be removed; otherwise the activity is soon brought to a standstill.

The increased blood-flow tends on the one hand to lower the general arterial blood-pressure, but on the other increases the supply of venous blood to the heart, so that the latter can fill more rapidly. Carbon dioxide and lactic acid probably act on the heart or augmentor centre in a manner similar to their action on the respiratory centre, and the increased respiratory movements themselves aid the circulation. The various factors which come into operation are not yet clearly understood, but the result is that the rate of blood-flow is evidently greatly increased. Both the amplitude and frequency of the heart's beats are greater during or just after muscular exertion, and the arterial blood-pressure greatly increases, in spite of the increased rate of escape of blood from the aorta, and the controlling action of the cardio-inhibitory centre. Similar circulatory phenomena are observed if air is breathed in which carbon dioxide has been allowed to accumulate to such an extent as to cause panting, or if the oxygen percentage in the air falls rapidly.

Using a quite new method, Krogh and Lindhard* have recently found that the flow of blood through the lungs in man varied from about 3 litres per minute, during rest, to about 21 litres during work which was by no means maximal. The increased blood-flow is

* *Skand Archiv f. Physiol.*, xxvii., p. 100, 1912.

thus comparable to the increased pulmonary ventilation and rate of respiratory exchange, which may be increased to about fifteen times during very severe muscular work.

It might perhaps be expected that forced breathing would lead to an arrest of the heart, similar to the arrest of respiration in apnœa. In man, in short experiments, no such arrest, and no very marked fall of blood-pressure appears to occur, though this does not exclude a considerable slowing of the circulation. Yandell Henderson has shown, however, that prolonged excessive artificial respiration by inflation leads in animals to stoppage of the heart, and that this is dependent, mainly at least, on absence of carbon dioxide.

In considering the relations of the circulation to respiratory exchange, we must bear in mind that, although the supply of oxygen and removal of carbon dioxide is always one of the most pressing of physiological necessities, the circulation has many other functions to perform than these. For instance, the circulation through the skin is probably chiefly concerned with the regulation of body temperature, including supply of water to the sweat-glands. In the case of the salivary glands, where during their maximum activity the blood comes through of a bright red arterial colour, the supply of water by the blood seems to be all-important. In other organs the exchanges of sugar, urea, salts, and all the countless substances carried to and fro in the body by the circulation, have also to be considered. With respect to this whole subject our knowledge is as yet very meagre, largely because attention has been so exclusively directed to the physics as distinguished from the physiology of the circulation, and under the influence of physical theories of life the circulation has, from the time of Descartes onwards, and contrary to the far sounder ideas of Harvey, been to a large extent regarded as determining, rather than as determined by, physiological activity.

## II. ABNORMAL INTERFERENCE WITH RESPIRATION.

Under abnormal or pathological conditions the conveyance of oxygen and carbon dioxide between the external air and the tissues may be interfered with in a great variety of different ways, and sometimes in more than one way at the same time. Unfortunately, clinical and experimental data for the correct understanding of many kinds of respiratory abnormality are still lacking, so that in the following pages conjecture has sometimes to take the place of established fact, and various forms of respiratory disturbance are passed over without proper discussion. An attempt is, however, made at a systematic treatment of the subject.

In whatever way the interference may be brought about, it may give rise to either excess or deficiency of the carbon dioxide partial

pressure within the body. The possibility of deficiency must be recognized as well as that of excess, since hyperpnœa from some other cause than accumulation of carbon dioxide would evidently, from the foregoing account, lead to abnormal deficiency of carbon dioxide, and this condition might or might not be harmful. The interference may also produce deficiency of oxygen, and, as a matter of fact, oxygen deficiency is a very common result. The oxygen-supply to the body may also be increased beyond normal. A general account of the symptoms produced by excess or deficiency of carbon dioxide or oxygen will first be given.

**Effects of Excess of Carbon Dioxide.**—The effects produced by excess of carbon dioxide alone can be observed best in man when air containing excess of carbon dioxide is breathed, precautions being taken, if necessary, to prevent any want of oxygen. If the same air is simply rebreathed continuously, the carbon dioxide in it being allowed to accumulate, the breathing at first simply becomes deeper and deeper, the increased depth being very nearly sufficient to keep the alveolar carbon dioxide percentage constant. When about 3 per cent. of carbon dioxide is present in the inspired air, the increased depth of breathing becomes just subjectively noticeable during rest. On exertion, however, the unusual hyperpnœa is very noticeable, and the power of doing any hard work is much impaired by the hyperpnœa. The reserve of respiratory power which normally exists during rest has evidently been considerably drawn on, so that the increased respiratory demands during work cannot be met so far as carbon dioxide is concerned. This condition is comparable to that met with in cases of heart disease, anæmia, etc., where any exertion leads to excessive respiratory distress. With about 4 per cent. of carbon dioxide the deep breathing becomes very appreciable, and the frequency of breathing may begin to increase; the pulse also becomes stronger and more frequent, so that the general condition resembles that produced by some moderate muscular exertion, such as walking. The alveolar carbon dioxide percentage is still only increased by about 0·5 per cent.

With further rise in the carbon dioxide of the inspired air, the panting rapidly becomes excessive, both depth and frequency of breathing being greatly increased. The increased ventilation of the lung alveoli and rate of circulation can no longer even approximately compensate for the increased partial pressure of carbon dioxide in the alveolar air, so that with about 6 per cent. of carbon dioxide in the inspired air there is great distress. This is often accompanied or followed by headache. With much further increase, symptoms of mental confusion appear, which pass into loss of consciousness. The toxic action of high percentages of carbon dioxide quiets the respiration and cardiac pulsations, and owing to this effect on animals the normal physiological effects of carbon dioxide

on the respiration, etc., were almost entirely missed by earlier physiologists.

About 25 per cent. of carbon dioxide seems to be required to cause death within a moderate time in mammals, but 50 per cent. may be breathed for a short time. When air is rebreathed continuously from a large bag or other closed space of fair capacity, the symptoms are entirely due to carbon dioxide up to the point of extremest hyperpnœa. Want of oxygen, which would ultimately cause death, tells only at a later stage; and there are no other harmful substances in the respired air.

It is very seldom that death, or even severe symptoms, from carbon dioxide poisoning, come under observation in man. The deaths in mines, wells, etc., which are commonly attributed to this cause are due almost invariably to want of oxygen or carbon monoxide; and though carbon dioxide may also be present in moderate percentages, it only tends to avert death, since it stimulates the breathing and circulation. Men are not apt to go accidentally into air containing much carbon dioxide, since the presence of the gas is at once perceived by the choking sensation and panting which it produces. An interesting case in which men often suffer from the pure effects of carbon dioxide is that of divers. If, as often happens owing to ignorance of the physiological conditions or leaky air-pumps, a diver working at some depth has an air-supply just sufficient to enable him to keep his alveolar carbon dioxide pressure normal during rest, it is evident that if he begins to exert himself, and thus increase several times his production of carbon dioxide, the air passing through his helmet will rapidly become so charged with the gas that its partial pressure in his alveolar air rises to 10 per cent. of an atmosphere or more. As a consequence he has a struggle for breath, often ending in complete loss of consciousness. His condition is not directly dangerous, however, as he has plenty of oxygen, the partial pressure of this gas being probably far above normal owing to the high atmospheric pressure. A little consideration will show that, in order to enable a diver to work at any given depth, his minimum air-supply (measured at atmospheric pressure) must be increased in exact proportion to the barometric pressure of the air he is breathing. In the British Navy precise regulations on this point are now laid down for divers working at various depths.*

Except where the breathing is actually obstructed, as in asthma, etc., the effects of any considerable excess of carbon dioxide are seldom observed under pathological conditions, since, as will be explained more fully below, they are almost completely masked by the effects of want of oxygen, which will now be considered.

**Effects of Deficiency of Oxygen.**—The effects of want of oxygen, whether rapidly or slowly produced, continued for long or short

* *Report of the Committee on Deep-Water Diving*, Parliamentary Paper (C.N. 1509), 1907.

periods, slight or extreme, come very frequently under observation in man, are brought about in a variety of different ways, and are almost protean in their manifestations.

The effects of breathing air partly or wholly deprived of its oxygen may first be considered. If an atmosphere consisting wholly of a physiologically indifferent gas, such as nitrogen, hydrogen, or methane, be breathed, loss of consciousness occurs suddenly, and practically without warning, within about forty-five seconds during rest, or probably more quickly during exertion. The store of oxygen in the alveolar air is washed out, and even the venous blood gives off its oxygen by diffusion into the alveoli, so that the effect is very rapid—far more so than drowning. Loss of consciousness is quickly followed by convulsions, with a temporary rise of blood-pressure, and respiratory struggle, ending very shortly in cessation of the breathing, and succeeded a few minutes later by cessation of the heart-beats and death, unless artificial respiration of air is applied. The effects of sudden want of oxygen in the higher centres are seen also in ordinary fainting, which is due to a rapid fall in arterial blood-pressure, and consequent failure in the oxygen-supply to the brain.

Some parts of the body, such as the muscles or limbs, will tolerate complete deprivation of oxygen for a considerable time without injury, as when a tourniquet is applied to a limb. Other parts, such as glands, or particularly the central nervous system, are quickly injured; and the injuries may be irreparable. It has been found in animals that the brain will not recover after the circulation has been completely blocked for about ten to fifteen minutes.* It is also the brain which usually recovers most slowly, if it recovers at all, in cases where the oxygen-supply has been greatly restricted for some time, as often happens in carbon monoxide poisoning.

When want of oxygen occurs more gradually, but within a few minutes, as in breathing air with a pretty rapidly diminishing percentage of oxygen, there is usually much hyperpnœa and air-hunger, accompanied by marked cyanosis, before consciousness is lost. The amount of hyperpnœa preceding loss of consciousness seems to vary considerably in different persons, however, some persons having very little. As a rule the hyperpnœa begins to be just noticeable when the oxygen percentage in the inspired air falls to about 14 or 12 per cent., and becomes pretty appreciable at 10 per cent. From this point on, cyanosis of the lips, ears, etc., becomes increasingly evident, while the hyperpnœa becomes more and more marked, along with increase in pulse-rate, rise in blood-pressure, and subjectively appreciable throbbing of the heart and arteries. At about 5 per cent. of oxygen the cyanosis is very great, and consciousness begins to fail rapidly.

* Stewart, Guthrie, Burns, and Pike, *Journ. of Exper. Med.*, 1906, p. 300; 1908, pp. 371, 470

When the want of oxygen occurs more gradually—in the course of, say, half an hour—the phenomena are very different. The breathing again begins to be somewhat deeper at about 14 or 12 per cent. of oxygen, but the increase is slight, and not subjectively appreciable. Cyanosis begins to appear distinctly, however, and is usually very well marked, at 10 per cent., though there is still little or no subjectively appreciable hyperpnœa. Marked symptoms of mental incapacity are, however, present. The memory of what is happening becomes very defective, and simple observations or calculations become impossible. Some persons may lose consciousness at about this point, but in most persons the oxygen percentage falls 1 or 2 per cent. lower before consciousness is lost. In any case, there is very little precedent air-hunger or hyperpnœa, so that loss of consciousness occurs without any struggle. Evident hyperpnœa may develop at a later stage, after consciousness is lost; but death occurs gradually and peacefully, to judge from observations on animals and in cases of carbon monoxide poisoning in man.

It will thus be seen that the immediate symptoms produced by want of oxygen differ greatly according to the rate at which the want of oxygen is produced. The explanation of these differences has already been referred to in connection with the regulation of breathing. Consciousness usually fails when the alveolar oxygen percentage falls to about four.

It has already been remarked that lactic acid may be formed in the tissues (including, doubtless, the respiratory centre itself) during exposure to want of oxygen, and that the presence of this acid, and its action on the respiratory centre, affords a possible explanation of the influence of want of oxygen in lowering the carbon dioxide threshold. How far this lowering effect may go before death occurs is not yet known. In a case of long exposure to carbon monoxide with loss of consciousness, the writer has observed very deep breathing similar to that seen in diabetic coma, where Beddard, Pembrey, and Spriggs,* have found as little as 1·2 per cent. of carbon dioxide in the alveolar air, owing to accumulation of oxybutyric acid in the blood. This and other observations suggest a possible great lowering of the carbon dioxide threshold, but actual analyses in man have not hitherto shown a lowering of more than about 3 per cent. Chiefly laboratory experiments have been made, however; clinical observations are still very sparse.

Hitherto mention has only been made of the more immediate effects of want of oxygen. Naturally, however, every part of the body and every physiological function is sooner or later affected by shortage in the oxygen-supply, such as occurs in prolonged exposure to air with a low percentage or partial pressure of oxygen, in carbon monoxide poisoning, great anæmia, heart disease, and other conditions. Serious restriction in the oxygen-supply seems, in general,

* *Journ. of Physiol.*, xxxvii., p. xl, 1908.

to bring about a condition of impaired function, accompanied by "cloudy swelling" and fatty degeneration, and is associated with œdema or capillary hæmorrhages due to injury or actual giving way of the capillary walls. Some of the more prominent symptoms in connection with different organs or functions must, however, be referred to.

Where the oxygen shortage is not sufficient to cause loss of consciousness, the most prominent symptoms are in connection with the central nervous system, and are often observed in partial carbon monoxide poisoning or during a stay at a very high altitude. One frequent symptom is headache, which is commonly accompanied by loss of appetite, nausea, and actual vomiting. In cases of carbonic oxide poisoning these symptoms are usually worse after return to fresh air. In any case, they take some time to develop, and a short exposure does not readily produce them. They are apt to last for some hours after the want of oxygen has been removed, and seem to be indicative of the temporary damage which has been produced by the shortage of oxygen. Another symptom is impairment of judgment and self-control. A man who is suffering from the effects of want of oxygen can hardly be regarded as responsible for his actions. He frequently shows symptoms very similar to those of alcoholic poisoning. Thus, he may become exhilarated, and begin to sing or shout; or very depressed, and burst into tears without the smallest reason; or extremely quarrelsome; or simply dull and sleepy. If he is in a position of danger, he may fail to take the measures which are evidently necessary for the safety of himself and those with him, even when he is well aware of the danger. This extraordinary impairment of judgment is extremely characteristic, and the person himself is totally unaware of it, and quite confident that his mind is absolutely clear. The memory of passing events and power of judging of the lapse of time are also greatly impaired. Often the time seems much longer than it really is. For instance, a man suffering from carbon monoxide poisoning may think he has gone a long way when he has only stumbled a few yards.

The senses are greatly impaired, particularly the sense of pain. It is a very common thing for miners affected by carbon monoxide to allow themselves to be severely burnt by their lamps; and there is also considerable danger of burning by hot-water bottles applied in the treatment of men suffering from the effects of want of oxygen. Perception is more affected than mere sensation. One sees things without being able to understand them properly. It is very hard, for instance, to read a simple instrument such as a barometer or gas analysis apparatus, or to make a colorimetric comparison, or properly understand print or writing. One also misjudges the positions of things, and goes stumbling about, often grasping at things which are some distance off. It is impossible to walk straight, however slowly. The sense of the position of the limbs seems to be

too much impaired. When the senses finally go, they seem to disappear in a certain order, the power of hearing being usually retained longest. Each sense also seems to go suddenly.

The power of voluntary movement is also greatly affected. In carbon monoxide poisoning inco-ordination of movements in walking, etc., is first noticed; then, quite suddenly, the power of voluntary movement of the legs is lost, and the person collapses. The same very sudden failure occurs in balloon ascents to great altitudes. Power over the arms survives for a short time, but also disappears suddenly. The power of moving the head may still be left, as in the case of Coxwell, when Glaisher and he had ascended in a balloon from Wolverhampton in 1862 to a height of about 29,000 feet. The limbs of both men were paralyzed, and Glaisher had lost his senses one by one. Coxwell was, however, able to grasp the valve-rope with his teeth and stop the ascent of the balloon, saving the lives of both men. In contrast to this was the case of Crocé-Spinelli, Sivel, and Tissandier, who ascended from Paris. Although provided with bags of oxygen, and warned by Paul Bert of the danger they were incurring, they were all paralyzed before they could raise the oxygen-tubes to their lips, and only Tissandier survived. Perhaps nothing illustrates better the extreme danger of any position in which men are exposed to the progressive effects of want of oxygen. Their judgment was evidently greatly affected, so that they went on reckless of the danger; and they were paralyzed quite suddenly. Exactly the same sequence of events is often seen in the case of rescuers at colliery explosions or fires. They probably know the danger of carbon monoxide, but do not act upon their knowledge, and paralysis comes rapidly when they have gone too far to allow of retreat or of their rescue by others.

It is difficult to judge as to how far the psychical abnormalities seen in cases of disease associated with shortage of oxygen are directly attributable to the want of oxygen—for instance, the psychical symptoms met with in anæmias of various kinds—but it seems not improbable that the want of oxygen is one cause of these symptoms.

There is some evidence that peripheral neuritis may be produced by repeated or more or less continuous exposure to want of oxygen. Cases of neuritis following exposure to carbon monoxide have, at any rate, been observed repeatedly, though the possibility of some other poisonous gas having been also present, and having caused the neuritis, cannot yet be definitely excluded.

Besides the nervous system, the heart is often prominently affected by exposure to want of oxygen, and particularly if the exposure is associated with muscular exertion throwing a strain on the heart. Rapid dilatation seems to occur, so that the mitral valves may become incompetent. Sometimes symptoms resembling those of acute valvular disease follow exposure to carbon monoxide

poisoning along with much exertion. In high mountain ascents it seems to be often the heart which gives way and produces dangerous exhaustion, and the cardiac troubles in anæmia are perhaps of the same nature, particularly when much physical exertion is continued in spite of the anæmia. Want of oxygen in the heart muscle must necessarily be increased by any exertion. A symptom due to cardiac failure gives the earliest warning of danger in progressive carbon monoxide poisoning. When no symptom is yet experienced during rest, it will be found that any considerable exertion is followed after about half a minute by faintness. The heart cannot respond to the extra call upon it to maintain the blood-pressure in spite of the increased flow of blood to the muscles, and consequently the blood-pressure falls.

A fact somewhat difficult to explain in connection with carbon monoxide poisoning is that exposure to cold is liable to produce sudden fainting and loss of consciousness. It commonly occurs that men who retire from the poisonous air to cool and fresh air suddenly lose consciousness or become much worse. It is well known also to mountain-climbers that certain positions, where temperature, wind, etc., are different from others at the same height, are much more apt to cause disablement than others. Thus, when the oxygen-supply is short, an apparently trifling cause may produce a great difference in the symptoms. The body has no reserve to fall back upon in compensating for these causes, and they therefore assume great importance. Similarly, a slight change towards more favourable conditions may be equally important in a favourable direction, as, indeed, is so often observed in the treatment of disease of any kind.

Various troubles in connection with the alimentary canal are associated with shortage of oxygen. Digestion is impaired, while diarrhœa or constipation seems also to be common. These troubles may be due to impairment by want of oxygen in the activity of the lining epithelium, digestive glands, or muscular coat of the alimentary canal.

When there is considerable shortage of oxygen, large quantities of lactic acid appear in the urine, as already mentioned. Glycosuria also occurs, and the nitrogenous metabolism seems to be markedly increased. All of these conditions are evidence of the great upset in general metabolism.

Albuminuria is often found, and may be attributed to affection of the kidney itself by the shortage of oxygen. The kidney and other glands are known to be very sensitive to want of oxygen.

As want of oxygen, particularly if it has existed for some time, causes definite damage to living tissues, symptoms of various kinds may remain for some time after the shortage of oxygen has ceased. The after-symptoms of exposure to great want of oxygen are often extremely formidable, particularly in the case of the central

nervous system. When consciousness has been lost for some time owing to lack of oxygen, it is often not regained till long after the normal oxygen-supply has been restored. In carbon monoxide poisoning, for example, a short time in pure air is sufficient to remove any immediate danger from want of oxygen; but often consciousness is not regained until many hours after the blood has returned to a normal condition, or it may not be regained at all. Sometimes recovery is rapid, but if the exposure has been long and serious the central nervous system has been damaged; and time must elapse before the damage can be repaired, if indeed it can be repaired at all. A great variety of symptoms are observed, and only a few of them can be referred to here. Often the limbs are in a more or less spastic condition, and convulsions may occur at intervals. When consciousness returns, the spastic condition of the muscles makes every voluntary movement extremely slow. Usually the mind is greatly affected for a time, and memory of the preceding events is lost, or statements as to what happened are quite unreliable. Even when the power of movement and locomotion is regained, the mental condition may be quite abnormal for a long time. Sometimes the patient has to be confined in an asylum. As a rule, however, complete recovery occurs sooner or later, unless death has taken place within two or three days. Many of the symptoms are probably due to cerebral hæmorrhages.

Not infrequently pneumonia supervenes within a day or two of the exposure, and may prove fatal even after consciousness has been completely recovered. The cause of the pneumonia is somewhat obscure, but the frequency of its occurrence is perhaps an index of the precarious condition of the whole body for some time after it has been subjected to extreme want of oxygen.

**Effects of Diminished Atmospheric Pressure—Mountain Sickness.**—Although the effects of diminished atmospheric pressure, as usually observed, are identical with those of want of oxygen, the manner in which the symptoms are produced, and other circumstances connected with them, require separate discussion.

It has already been explained that under normal conditions the breathing is so regulated as to keep the partial pressure of carbon dioxide in the alveolar air constant. At normal atmospheric pressure the total pressure in the alveolar air is 760 millimetres of mercury. As the air is saturated with moisture at the body temperature, 47 millimetres of this pressure are due to moisture, and the remaining 713 millimetres to oxygen, carbon dioxide, and nitrogen. As this air contains about 14·2 per cent. of oxygen (a reduction of 6·7 per cent. from the percentage in pure air) and 5·6 per cent. of carbon dioxide, the partial pressures of these two gases are about $\frac{14{\cdot}2}{100} \times 713$ and $\frac{5{\cdot}6}{100} \times 713$, or 101 and 40 millimetres respectively. Let us see now what must happen if the atmosphere pressure is

reduced to half, and the partial pressure of carbon dioxide is still kept constant by the breathing. The total barometric pressure is now 380 millimetres, or 333 millimetres when the pressure of aqueous vapour is deducted. The pressure of carbon dioxide is 40 millimetres, which corresponds to 12·0 per cent. of carbon dioxide in the dry alveolar air. The oxygen percentage will be reduced parallel with the increase of carbon dioxide, and will now be about $20{\cdot}9-\left(12{\cdot}0\times\frac{6{\cdot}7}{5{\cdot}6}\right)=6{\cdot}5$ per cent. Its partial pressure will thus be only $\frac{6{\cdot}5}{100}\times 333=21{\cdot}6$ millimetres. This pressure corresponds to that of air containing only 3·0 per cent. of oxygen at normal pressure, and we have already seen that consciousness would be lost if the alveolar oxygen pressure went so low, whereas in actual practice there is usually no loss of consciousness at a pressure of 380 millimetres.

The above example will show at once that the normal method of regulating the breathing must break down at low pressures. The physiological action of oxygen and other gases, as we have seen, depends upon their partial pressures; and with diminished barometric pressure the partial pressure of oxygen soon becomes so low that want of oxygen is produced. There is not a shadow of doubt that the whole train of symptoms produced by the low atmospheric pressures met with at high altitudes depend primarily on want of oxygen, as Paul Bert first proved experimentally. The mechanical effects are nil, since the diminution of pressure is at once communicated equally to all parts of the body.

What actually happens is that, as soon as the pressure has fallen to a certain extent (usually to about 550 millimetres in short exposures), want of oxygen begins to tell on the breathing, and the threshold of alveolar carbon dioxide pressure is lowered, owing probably, as explained above, to diminished alkalinity of the blood. As a consequence the oxygen pressure in the alveolar air becomes higher than would otherwise be the case, and extreme want of oxygen is thus averted. Fig. 16 shows the mean variations in the alveolar oxygen and carbon dioxide pressures in two persons who were subjected to diminished atmospheric pressures in the steel chamber at the Lister Institute.* It will be seen that when oxygen was added to the air the alveolar carbon dioxide pressure remained normal, in spite of a diminution of the barometric to about 300 millimetres. When oxygen was not added, on the other hand, the alveolar carbon dioxide pressure began to fall rapidly after the barometric fell to about 550 millimetres. The fall in the alveolar oxygen pressure was thus checked, so that there remained more than 30 millimetres of oxygen pressure at the lowest barometric pressure reached.

* Boycott and Haldane, *Journ. of Physiol.*, xxxvii. 355, 1908; also Ogier Ward, *ibid.*, 378.

These experiments were comparatively short ones. When the exposure to low pressure lasts longer, the lowering of the alveolar carbon dioxide threshold is much more marked, and begins to manifest itself at less diminished barometric pressures. Thus, after about twenty-four hours' exposure in the chamber to a barometric pressure of 540 millimetres, a fall from 38·5 to 31 millimetres was observed; whereas in the short experiments just referred to, there was hardly any fall at this atmospheric pressure. In the longer experiment diminished alkalinity of the blood had doubtless

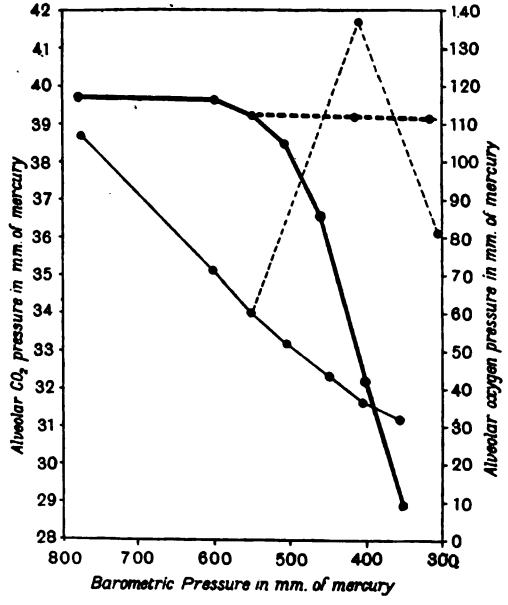



FIG. 16.—EFFECTS OF DIMINISHED BAROMETRIC PRESSURE ON THE ALVEOLAR GAS-PRESSURES.

The thick lines show the alveolar $CO_2$ pressure, and the thin lines the alveolar $O_2$ pressure. The dotted lines refer to the experiment in which oxygen was added to the air.

had sufficient time to develop. One reason why high balloon ascents are more dangerous than they otherwise would be at a given height is that there is not time for this condition to develop its full protective effect. That the blood actually becomes less alkaline at high altitudes was first shown by Galeotti.

It is evident that, if carbon dioxide in suitable proportion is added to the inspired air, a given partial pressure of oxygen in the inspired air will be less dangerous than would otherwise be the case, for the breathing will be stimulated, so that the oxygen pressure in the alveolar air is raised. At the same time the circulation will be stimulated by the slightly increased carbon dioxide pressure

in the blood, and this will increase the oxygen-supply to the tissues. If oxygen is breathed instead of air, a much lower barometric pressure can be borne than when air is breathed; and oxygen has been successfully employed in high balloon ascents, the height reached being much above that at which death or unconsciousness occurs when air only is breathed. The best results seem to be attained, however, when a suitable mixture of oxygen and carbon dioxide is breathed. The addition of the carbon dioxide does not sensibly lower the alveolar oxygen pressure, and stimulates the circulation, which latter fact is apparently a great advantage. Breathing a mixture of oxygen and carbon dioxide, Aggazotti* reached a barometric pressure of 120 millimetres (corresponding to nearly 50,000 feet above sea-level) in a steel chamber without losing consciousness. It is, however, a mistake to conclude with Mosso and Aggazotti, in view of the favourable effects of adding carbon dioxide to the inspired air, that all, or any, of the symptoms of mountain sickness are due primarily to deficiency of carbon dioxide ("acapnia"). As we have seen, all the facts are in accord with Paul Bert's conclusion that mountain sickness is due primarily to want of oxygen. The lowering of the carbon dioxide pressure in the alveolar air, and consequent lowering of the percentage of carbon dioxide in the blood, is due to the presence of acid, which takes the place of an equivalent proportion of carbon dioxide. There is thus no real acapnia in the physiological sense, and the normal proportion of carbon dioxide in the blood could not be artificially restored at a low barometric pressure without producing intense hyperpnœa.

In connection with attempts to reach great heights in balloons or very low pressures in steel chambers, it may be well to call attention here to the risks of caisson disease—a subject which will be discussed later.

It is interesting to compare the symptoms produced by fall in barometric pressure with the dissociation curve of oxyhæmoglobin. From what has already been said as to the causes of the passage of oxygen through the septum dividing the alveolar air from the blood, it follows that we can expect no numerical correspondence between the oxygen pressure in the alveolar air and that in the blood; and consequently we cannot predict the percentage saturation of the blood when we know the alveolar oxygen pressure. If the diffusion theory were correct, we should expect the oxygen pressure in the blood at low atmospheric pressures to be considerably below that in the alveolar air, particularly during muscular exertion. Actually, however, the difference is in the opposite direction, as already mentioned above.

The various symptoms produced by diminution of atmospheric pressure, although they have received the name of

* *Archives Italiennes de Biologie*, xliv., 1906.

" mountain sickness," are simply those of want of oxygen produced gradually. In the main they have been described above. Headache, nausea, loss of appetite, and general exhaustion, are very common. Both animals and men suffer, horses being very sensitive. Great mortality has often occurred in the case of armies crossing high passes under physically difficult conditions, and, at the best, mountain sickness may easily become a serious matter unless relief can be obtained by descending. The tendency to irregularity in the breathing, and to its assuming a periodic type at night, with much discomfort, has already been alluded to. Another characteristic fact is the unusual shortness of breath on exertion.

A further symptom is that any holding of the breath, with consequent lowering of the alveolar and arterial oxygen pressure, disturbs the respiratory centre sharply and produces panting, which may be followed quickly by shallow breathing or apnœa in consequence of the excessive reaction of the centre.

Persons who go to reside at places situated at a height of more than about 6,000 to 7,000 feet very commonly experience some discomfort at first, such as unusual shortness of breath on exertion, or disturbed sleep. At heights of over 10,000 feet these disturbances are more marked, and may amount to serious mountain sickness. After one or two weeks, or less, however, they usually pass completely away. It is said that in some of the towns high up in the Andes a new-comer may often be distinguished by his stopping frequently for breath when he walks about the streets. Where it takes a considerable time to reach high altitudes from the plains, as in the Himalayas, adaptation occurs during the journey, so that its occurrence is not so readily observed as in the Andes, or even at Alpine resorts. Mountaineers often suffer severely from mountain sickness if they go straight to high altitudes without becoming acclimatized at intermediate heights.

The physiological changes which occur at high altitudes, and particularly the adaptive changes, have been studied very carefully during a stay of five weeks on the summit of Pike's Peak, Colorado, by Douglas, Yandell Henderson, Schneider, and the writer.* The altitude is 14,100 feet, and the barometer about 457 millimetres or 18 inches. Many persons came up by the cog-wheel railway or on foot, so that there was abundant opportunity for observation. In practically all new-comers the lips and skin were more or less bluish, and as a rule nausea, headache, etc., developed within a few hours in those who stayed. A few became faint, dizzy, and very blue within half an hour of their arrival, and breathing pure oxygen was found to relieve these symptoms at once. All were very short of breath on exertion. Periodic breathing was frequently observed in ourselves during the first few days, and was promptly abolished on breathing oxygen, in accordance with the explanation already given of periodic breathing.

* *Phil. Trans. Roy. Soc.*, 1912.

After a stay of two or three days on the summit, the blueness of the face and symptoms of mountain sickness disappeared gradually and completely. The tendency to periodic breathing also diminished greatly, and the hyperpnœa and discomfort on muscular exertion became less. There could thus be no doubt that a process of acclimatization had occurred, and after the first eight or ten days we all felt and looked extremely well.

It was found that the partial pressure of carbon dioxide in the alveolar air had fallen from about 40 millimetres at sea-level to 27 millimetres ; in other words, the alveolar ventilation for a given quantity of carbon dioxide produced had increased about 50 per cent. This increase in the breathing raised the alveolar oxygen pressure considerably above what it would otherwise have been, but could not account for the disappearance of the mountain sickness and blueness of the face, since nearly the whole of the increase in breathing was present from the time of our arrival on the summit, and the remaining part developed gradually—chiefly after the blueness, etc., had completely disappeared.

The oxygen pressure of the alveolar air was about 52 millimetres (6·8 per cent. of an atmosphere), corresponding, on the dissociation curve (Fig. 15), to 83 per cent. saturation of the hæmoglobin. As, however, the alveolar carbon dioxide pressure was only 27 millimetres it might have been expected that the curve for the arterial blood on Pike's Peak would be shifted to the left. In experiments on the Peak of Teneriffe, Barcroft had already found, however, that there is no such shifting of the curve, since the effect on the hæmoglobin of the diminished carbon dioxide pressure is exactly compensated by the diminished alkalinity of the blood. Our experiments confirmed this, showing that in presence of 27 millimetres of carbon dioxide pressure the curve of blood at Pike's Peak was exactly the same as that of blood at Oxford in presence of 40 millimetres. Blood saturated on Pike's Peak with alveolar air outside the body, but at body temperature, had also a distinctly dark appearance, contrasting with the red lips of the subjects from whom the blood was taken.

On investigating the arterial oxygen pressure, this was found to be, during rest or gentle work after acclimatization, about 35 millimetres above the oxygen pressure of the alveolar air. This observation accounted at once for the bright red colour of the lips and disappearance of mountain sickness. The epithelium of the lung alveoli was actively secreting oxygen inwards, whereas at sea-level no such secretion occurs during rest, as has already been explained. An experiment made on a subject who had first come up, and who had blue lips, and shortly afterwards had the usual symptoms of mountain sickness, showed that his arterial oxygen pressure was but little above that of the alveolar air, whereas, two days later, when he had recovered and become acclimatized, his arterial oxygen

pressure was much in excess. It thus appears that the main factor in acclimatization is the development of a power of actively secreting oxygen inwards, even during rest.

It has been known for long that at high altitudes the blood gradually becomes richer in hæmoglobin and corpuscles. The same phenomenon is observed in animals exposed to a low oxygen percentage in the air at sea-level, or to chronic poisoning with carbon monoxide: also in cases of heart disease, etc., accompanied by cyanosis. In a case of cyanosis from congenital pulmonary stenosis, Douglas and the writer found the hæmoglobin percentage as high as 180. There is thus no doubt that increase in the hæmoglobin percentage is a natural adaptive reaction to want of oxygen. In persons who had lived for some weeks on Pike's Peak the hæmoglobin percentage varied from 115 to 154 per cent. by the Gowers-Haldane scale, and the increase in percentage of corpuscles was in the same proportion. In the cases observed there the increase was very gradual for two or three weeks. In another case (recorded in the same paper) observed in the Andes the increase was very rapid, averaging 8 per cent. daily for four days on going to an altitude of 12,500 feet. It was found on Pike's Peak that the slow increase in hæmoglobin percentage was accompanied by a very marked increase in the total hæmoglobin in the body, and a slight increase in blood-volume; in other words, the change was not due merely to concentration of the blood previously existing, but was accompanied by new formation of red corpuscles. In correspondence with this conclusion Zuntz and his collaborators* had previously found that the red bone-marrow is increased in amount in dogs kept at high altitudes. On descending from Pike's Peak the hæmoglobin percentage dropped rapidly to normal; but the total hæmoglobin in the body took several weeks to return to normal. The diminution in the hæmoglobin percentage had thus been brought about at first by a dilution of the blood with plasma, and it is probable that in cases where the hæmoglobin increases rapidly on going to a high altitude, the increase is brought about at first by a corresponding abstraction of plasma from the blood.

In the case of congenital heart disease just referred to, the blood-volume was doubled, and the total hæmoglobin increased nearly four times. At altitudes higher than Pike's Peak something similar might perhaps occur.

It is a very significant fact that although the colour of the arterial blood was normal, and the percentage of oxygen carried by it was considerably above normal, the body still showed marked reactions to want of oxygen, since even after acclimatization the alveolar carbon dioxide pressure remained low, and the hæmoglobin percentage high. These conditions are found, though to a smaller extent, in persons living at much less high altitudes above sea-level.

* Zuntz, Loewy, Müller, and Caspari, *Höhenklima*, Berlin, 1906.

A subnormal percentage of hæmoglobin has also been found by Börnstein in animals kept in compressed air, and by the writer in men who had been working daily with mine rescue apparatus, breathing nearly pure oxygen. On the other hand, there is no diminution in the alveolar oxygen pressure in cases of ordinary anæmia, where the oxygen carried by the arterial blood may be diminished to a third. From all these facts it seems evident that the partial pressure of oxygen in the arterial blood is a factor of great importance, apart altogether from the amount of oxygen in combination with hæmoglobin. The body seems to be sensitive to a very small diminution in the normal arterial oxygen pressure—probably because the oxygen pressure is required for the oxidation of substances other than hæmoglobin, which are carried to the lungs by the venous blood. An increased hæmoglobin percentage at high altitudes may help the oxidation of these substances, or prevent their formation, by maintaining in the tissues a higher oxygen pressure than would otherwise be the case.

The cause of the diminished alkalinity of the blood at high altitudes is not yet clear. The degree of fixed alkalinity in the blood is presumably regulated by the kidneys, and appears to be in inverse ratio to the pressure of carbon dioxide, these two factors varying, very probably, in such a way as to keep the hydrogen ion concentration about constant. As it takes many days for the alveolar carbon dioxide to reach its final pressure after ascending to a high altitude, or descending again to sea-level, there appear to be strong reasons for suspecting that the regulation of fixed alkalinity by the kidneys is physiologically connected with the sufficiency of the oxygen-supply to the body, and undergoes slow adaptive changes similar to those in the activity of the alveolar epithelium. Temporary disturbances in blood-alkalinity, such as those due to lactic-acid production during muscular work, are compensated for within an hour.

During prolonged and heavy muscular work on Pike's Peak, as in climbing, we noticed that even after acclimatization the lips became distinctly dark, but cleared up again rapidly on resting. The oxygen requirements were apparently so great that the alveolar epithelium could no longer maintain the arterial oxygen at its ordinary level, possibly owing to fatigue of the epithelium. The hyperpnœa was also in excess of what could be accounted for by the fact that the normal alveolar carbon dioxide pressure was reduced to 27 millimetres.

The circulation during rest appeared to be about normal after acclimatization. The total respiratory exchange during rest or work was also practically the same as at sea-level, and general health and mental faculties appeared to be quite unimpaired.

**Causes of Want of Oxygen and Cyanosis.**—It is desirable to review at this point the various causes which bring about a defective

oxygen-supply to the tissues, or cause blueness of the lips, tongue, and skin. The simplest and most direct of these causes is deficient saturation of the arterial blood with oxygen, owing to the partial pressure of oxygen in the alveolar air being too low. This, in its turn, may be due to deficiency in the oxygen pressure of the inspired air, or to deficient breathing caused by mechanical conditions, or diminished excitability of the respiratory centre owing to the influence of anæsthetics or other poisons. The deficient saturation may also be due to exudations or thickening of the alveolar walls, and consequent interference with the passage of oxygen inwards to the blood. Or part of the blood may be passing through portions of the lung which are blocked or collapsed, although the absence of cyanosis in many cases where large proportions of lung substance are blocked shows that very little of the pulmonary blood can be passing through the blocked parts. In cases, if they exist, where blood is passing directly from the right to the left side of the heart, there must also be some cyanosis.

Want of oxygen and cyanosis may also be due to the blood-flow being so slow that an abnormally large proportion of the oxy-hæmoglobin is dissociated as the blood passes through the capillaries. If the capillaries and veins are distended, and particularly if the hæmoglobin percentage is high, the colour of the lips, etc., is blue; but if there is no distension, the colour is more leaden. Blueness of the skin is, however, no certain index of reduced blood-supply to internal organs. When the skin is cold, for instance, it becomes more or less blue on account of very great local diminution of blood-supply. This diminution is a perfectly normal reaction, protecting the body against the excessive loss of heat which would otherwise result. The cyanosis so often seen in heart disease, etc., is probably also due largely or wholly to a protective restriction of the skin circulation, so that more important parts of the body receive a sufficient supply of blood.

Another cause of want of oxygen is interference with the oxygen-carrying of the hæmoglobin. When this is due to carbon monoxide poisoning, there is, of course, no cyanosis. When, however, the interference is due to the formation of methæmoglobin or other dark-coloured compounds, the apparent cyanosis is very striking, and may be out of all proportion to the actual deficiency in the oxygen-supply. If the cyanosis were due to the presence in the arterial blood of reduced hæmoglobin, the oxygen pressure in the blood would necessarily be very low; but with cyanosis due to the presence of methæmoglobin, etc., the oxygen pressure may be perfectly normal, and the supply of oxygen to the tissues quite free as a consequence.

Another possible cause of want of oxygen in the tissues is a shifting of the dissociation curve to the left (in Fig. 15). A shifting in this direction might reduce very greatly the oxygen pressure in

the tissues, so that great want of oxygen would arise without marked cyanosis. Such a shifting occurs when the carbon dioxide pressure of the blood is reduced by excessive breathing, provided there is no compensatory decrease of alkalinity. A similar shifting might be caused by excessive alkalinity of the blood, and does occur in carbon monoxide poisoning, thus adding to the effects of this gas. An abnormality in the salts of the red corpuscles, or in the concentration within them of hæmoglobin, might have a similar action, though as yet nothing is known on this subject. On the other hand, if the dissociation curve were shifted to the right by diminished alkalinity (not compensated for by diminished pressure of carbon dioxide) a condition of cyanosis might coincide with a perfectly free supply of oxygen to the tissues.

**Effects of Deficiency of Carbon Dioxide.**—As we have seen, the presence of carbon dioxide at a certain partial pressure plays the leading part in the regulation of breathing, and at any rate an important part in regulating the circulation. Its presence at a certain partial pressure may also be very important with regard to other physiological processes, although at present we know much more about the harmful effects of excess of carbon dioxide than about the effects due to its deficiency. In excess it undoubtedly acts as a tissue poison on all protoplasm, even the yeast organism being apparently paralyzed by its presence at a sufficient partial pressure. Almost the only very definite knowledge as to any immediate effects from its deficiency is derived from a study of the respiratory centre, which ceases to respond rhythmically in its usual manner unless the partial pressure of carbon dioxide exceeds a certain definite amount, just as the retina ceases to respond unless the stimulus of light exceeds a certain intensity.

The idea that deficiency of carbon dioxide ("acapnia") may be an important factor in the production of abnormal conditions was first put forward by Mosso in connection with his theory of mountain sickness, which has already been criticized above. More recently Yandell Henderson* has argued that the phenomena of "shock" are brought about by deficiency of carbon dioxide. He found that by excessive artificial respiration with an effective bellows arrangement he could produce in animals a condition in which the heart-beats became progressively more frequent and feeble, the blood-pressure fell, and death finally occurred; whereas if carbon dioxide was added to the air the animal survived. He also furnished evidence of the important local action of carbon dioxide in preventing paralysis of the circulation and venous stasis in the bloodvessels of the intestines. He believes that "shock" is ordinarily brought about by excessive respiratory movements due to nervous stimulation, or to the excitatory effects of anæsthetics on the respiratory centre, a state of acapnia being thus produced.

* *Amer. Journ. of Physiol.*, xxi., xxiii., xxiv., xxv., xxvi., and xxvii., 1908-1910.

It is undoubtedly the case that excessive excitation of nerves will produce hyperpnœa, and this may go on till the heart and circulation are seriously affected, just as with excessive artificial respiration. If the excitation ceases apnœa will be produced, and may be fatal. Henderson also finds that an insufficient dose of ether produces excitement, accompanied by excessive breathing and consequent acapnia. If the dose of anæsthetic is afterwards increased, so as to produce anæsthesia, sudden stoppage, not merely of the respiration, but also of the heart, may occur. The condition of acapnia seems to render the heart much more liable to stop under the influence of the anæsthetic than when the anæsthetic is from the outset given in sufficient doses to prevent acapnia. An anæsthetic may easily produce apnœa by rapidly diminishing the excitability of the respiratory centre, so that the existing partial pressure of carbon dioxide is insufficient to keep it in action. This is, however, much less serious than the stoppage of the heart, predisposed to by a condition of acapnia previously induced.

Ewald * showed many years ago that positive artificial ventilation of the lungs, so as to produce apnœa, causes the venous blood to become much less rich in oxygen. At that time apnœa was supposed to be produced by excess of oxygen, and there was a very slight excess of oxygen in the arterial blood. But as the venous blood contained much less oxygen than normally, there can be no doubt that the oxygen-supply to the tissues was, as a matter of fact, greatly restricted in consequence of diminished blood-flow. This may have been partly produced mechanically by the positive ventilation, or it may have been due to constriction of arterioles and diminished cardiac activity in consequence of absence of carbon dioxide and oxygen, or, perhaps more probably, to both causes combined. We do not know as yet what the various factors are which produce the condition which follows excessive artificial respiration.

Voluntary forced breathing in man causes after a minute or more marked abnormal symptoms in many persons. There is a feeling of stupor suggestive of that produced by slowly progressive want of oxygen. At the same time tingling ("pins and needles") of the hands, accompanied by cutaneous anæsthesia, is experienced, and marked contractures of groups of muscles occur. The pulse and blood-pressure may, however, be little affected. The colour of the skin is normal, and remains so until the subsequent apnœa is terminated by the arterial blood becoming of a venous colour, so that the respiratory centre is excited by want of oxygen in combination with the accumulating carbon dioxide. The phenomena are strongly suggestive of local diminished circulation, and consequent want of oxygen, in parts of the central nervous system. Voluntary forced breathing has sometimes been used by dentists for producing temporary anæsthesia.

* *Pflüger's Archiv*, vii. 575, 1873.

It may be that all the serious effects of acapnia from excessive breathing are reducible to the effects of want of oxygen in the central nervous system and heart, this want of oxygen being dependent partly on diminished circulation, and partly on the effects of diminished carbon dioxide in shifting the dissociation curve of oxyhæmoglobin in the manner already referred to above.

**Effects of Excess of Oxygen.**—Within wide limits, excess of oxygen has no effect at all on the breathing or respiratory exchange under normal conditions. Whether the oxygen percentage in the inspired air is raised, or the partial pressure of oxygen is raised by increasing the barometric pressure, the alveolar carbon dioxide pressure remains absolutely normal. Nor is there any appreciable change in the consumption of oxygen. The respiratory exchange of a living organism is very different from the processes of oxidation in the inorganic world. The tissues take the oxygen they require, and leave the rest. This is not because the arterial blood is already saturated, and can carry no more oxygen to the tissues, but because their requirements are already met. As we have already seen, the arterial blood, when saturated with pure oxygen in the lungs, does carry considerably more oxygen, and in a very readily available form; and if from any reason, such as impaired circulation or carbon monoxide poisoning, shortage of oxygen exists in the body, the breathing of pure oxygen makes a great difference. It probably also makes some difference during very hard muscular work; for we have seen above that shortage of oxygen occurs in the muscles during such work, and that this becomes much more marked at high altitudes, where the arterial blood is not so completely saturated as usual. It has been remarked that men seem to do hard work more easily in compressed air, as when compressed air is used in making tunnels under rivers.

At very high partial pressures oxygen has a poisonous effect, which was first noted by Paul Bert.* He found that at anything exceeding about three atmospheres' pressure of pure oxygen, or fifteen atmospheres' pressure of air, animals go into convulsions and die; and that oxygen at high pressure seems to be poisonous to all kinds of living organisms, although we know that the cells lining the swim-bladder of fishes can remain healthy in presence of a pressure exceeding 100 atmospheres of pure oxygen.

It was discovered more recently by Lorrain Smith† that exposure to a high partial pressure of oxygen produces pneumonia, and that this occurs at much lower partial pressures than are needed in order to affect the central nervous system in the manner discovered by Paul Bert, although the action on the lungs is slower. At a little less than three atmospheres' pressure of oxygen pneumonia was produced in about three hours, and the time required increased as

* *La Pression Barométrique*, 1878.

† *Journ. of Physiol.*, xxiv. 19, 1899.

the pressure of the oxygen was lowered. It was still produced, however, with oxygen at ordinary pressure; and even when only 75 per cent. of oxygen was present at ordinary pressure, death from pneumonia occurred in animals after four days' exposure. The lungs are, of course, exposed to the full partial pressure of the oxygen, while the rest of the body is more or less protected by the great fall of oxygen pressure which occurs in the systemic capillaries owing to the oxygen being used up.

It thus appears that long-continued breathing of pure oxygen may cause irritation of the lungs, passing into pneumonia. Fortunately, the incipient pneumonic condition is very quickly recovered from when ordinary air is again breathed; but the local effects of oxygen must be borne in mind when pure or nearly pure oxygen has to be administered for more than a short time to patients. A few hours' breathing of nearly pure oxygen does not seem to cause any harm to healthy persons, to judge from experience with mine-rescue apparatus. It is possible that pure oxygen may possess curative properties in virtue of its local action, if this is not too severe. The reported beneficial action of exposure to compressed air in cases of asthma might, for instance, be of this nature, and seems well worth further investigation.

**Mechanical Interference with Respiratory Movements.**—The respiratory movements may be interfered with mechanically by a variety of causes, either inside or outside the body. The pressure required to do so is comparatively slight, since the chest walls can only overcome a small adverse pressure. Thus, it is hardly possible to breathe against a difference of pressure within and without the lungs of a foot of water ($\frac{1}{2}$ pound to the square inch). A diver standing with his helmet about a foot below water is unable to breathe if the air in his helmet is at atmospheric pressure. Numerous cases are on record of persons being simply asphyxiated by the pressure of a large crowd, and the frequent overlaying of infants is well known. Hindrances to breathing more usually occur from some internal cause, however, such as asthma or bronchitis, or obstruction of the larynx or trachea, or pleural effusion, or pneumothorax. With complete or nearly complete obstruction, death of course occurs within a few minutes from want of oxygen.

If the hindrance arises from obstruction in the larynx or bronchi, the respirations are prolonged, while their amplitude may be normal, or even increased. The action of the vagus nerve naturally tends to produce this result under the circumstances. If, on the other hand, the amplitude is limited, as in pneumothorax, where the air in the affected pleural cavity may be under pressure, owing to a valvular opening, the frequency will be increased. Matters may become further complicated by exhaustion of the expiratory muscles, which are little used under normal conditions, and by hindrance to the circulation owing to increased intrathoracic pressure. In

asthma, for instance, the expirations are specially ineffective and prolonged, and the chest is very full of air.

Obstruction to the breathing must cause a distinct rise in the percentage of carbon dioxide in the alveolar air, causing intense air-hunger and distress. Unless the obstruction is very great, the alveolar oxygen percentage will not fall so low as to produce want of oxygen. Little or no immediate relief can thus be expected from administering oxygen. It may be, however, that some of the bronchi are almost completely blocked, so that the proper oxygenation of the blood is seriously interfered with. In this case, or where the circulation is also interfered with, oxygen will doubtless produce some relief.

It seems probable that in pneumothorax, where one lung is completely collapsed, the pulmonary circulation through the collapsed lung is also blocked, as the blood-pressure in the alveolar capillaries of the collapsed lung will immediately rise, and divert the blood-stream to the other lung. But for this, marked cyanosis would necessarily accompany pneumothorax. The remaining lung, if its movements are not too much hampered by the increased intra-thoracic pressure, can of course very easily perform the functions of both lungs during rest. Even if, owing to extensive consolidation of pleural effusion, only a fifth of the normal volume of lung were left functionally active, the demands made upon it during rest would be no greater than during ordinary continuous exertions under normal conditions, provided that the pulmonary circulation was blocked in any collapsed portions of lung, so that no unaerated blood passed through to the arterial side.

When violent expiratory efforts are made, as in very acute cases of bronchitis or whooping-cough, air may escape gradually from the air-passages or lungs. It may pass from the trachea into the neck, and down the arms, causing extensive subcutaneous emphysema, or still more easily into the pleural and peritoneal cavities. To judge from experiments on animals, it may also pass with considerable ease into the blood, in which case there must be serious risk of air embolism in some important part of the central nervous system. Ewald and Kobert * found that a pressure considerably less than the maximum expiratory pressure was sufficient to cause this escape of air. The production of pneumothorax or emphysema is thus a quite probable accompaniment of any condition in which the breathing is obstructed within the body, and probably a certain amount of pneumothorax would often be found if looked for carefully.

**Interference with the General Circulation.**—If the general circulation is slowed down—as must happen, for instance, in heart disease when compensation of one kind or another is not sufficient to maintain the normal blood-flow even during rest—it is clear that the

* *Pflüger's Archiv*, xxxi. 160.

oxygen-supply to the tissues must be rendered less easy, if not wholly insufficient. The blood will lose more than the usual proportion of oxygen in passing through the tissues, so that its mean partial pressure of oxygen will fall; and if this fall exceeds a certain amount, death must result. Increased breathing (although it may help the circulation considerably) cannot materially increase the amount of oxygen in the arterial blood, as the hæmoglobin is nearly saturated under ordinary conditions, and the amount of oxygen in simple solution could only be increased to a very slight extent by raising the oxygen pressure of the alveolar air even to that of the inspired air. The same remarks apply to conditions in which the circulation is impeded in the lungs from emphysema, etc., with failing compensation by the right ventricle.

It is very different, however, with carbon dioxide; for by increased breathing the amount of carbon dioxide can be lowered enormously, so that even with the diminished circulation there may be no undue accumulation of carbon dioxide in the tissues. Respiratory distress is thus relieved by increased breathing, but the shortage of oxygen still remains.

We have seen above that shortage of oxygen leads to diminished alkalinity of the blood, owing to accumulation of lactic acid and abnormal loss of alkali in the urine, and that this condition causes a lowering of the normal carbon dioxide threshold in the alveolar air and arterial blood. Such a lowering must occur in uncompensated cardiac cases, and its existence has been demonstrated by analysis of the alveolar air, particularly in cases of congenital heart disease with marked cyanosis.* In three congenital cases in young men, the alveolar carbon dioxide percentage varied from 3·0 to 4·8 per cent., as compared with the normal average of 5·6; while in three cases in young women it varied from 2·5 to 3·8, as compared with the normal average of 5·2. The compensatory increase in the hæmoglobin percentage was also well marked in these cases, the percentage by the Gowers-Haldane scale varying from 130 to 175. In most ordinary chronic cases the alveolar air was found to be normal during rest, indicating complete compensation under resting conditions. In several cases, however, where there were symptoms of failing compensation, the alveolar carbon dioxide was low, and in one case of a man as low as 2·6 per cent., or less than half the normal.† In this case there were severe symptoms during rest. On breathing oxygen the cyanosis diminished, the amount of air breathed was reduced very appreciably, and the pain also diminished. The effect of oxygen in rapidly relieving the breathing indicated that the hyperpnœa was not simply due to diminished alkalinity in the blood, but also to more direct action of oxygen want

* French, Pembrey, and Ryffel, *Journ. of Physiol.*, xxxix., p. ix, 1909; FitzGerald, *Journ. of Pathol.*, xiv. 328, 1910.

† Pembrey and Beddard, *Brit. Med. Journ.*, 1908, ii. 580.

on the respiratory centre, as is the case when air very poor in oxygen is breathed. Had the hyperpnœa been due merely to diminished alkalinity of the blood, the oxygen would have had no immediate effect on the breathing. As we have already seen, it takes a long time to bring back the alveolar carbon dioxide to normal if its reduction has been due simply to diminished alkalinity of the blood, and not to a direct action of the want of oxygen on the centre itself.

The lowering of the carbon dioxide threshold must, of course, diminish the range through which relief of respiratory distress can be obtained by increasing the breathing; for a point must be reached where the increased gaseous metabolism caused by great respiratory exertions must neutralize any relief which they might bring about. The work, and consequent increased metabolism, involved in breathing increases at a much more rapid proportional rate than does the increased lung ventilation.

It thus appears that the respiratory relief obtained by increased breathing in cases where the general circulation is interfered with is considerable, but still limited in amount, and that deficiency of oxygen, which may cause great cyanosis, is still present, in spite of the relief. Any lowering of the carbon dioxide threshold in the alveolar air is a sign of this deficiency. If compensation were seriously incomplete during rest, we might expect that a very slight exertion would easily cause a fatal fall of blood-pressure. In those congenital cases where cyanosis is dependent on direct passage of blood from the right to the left side of the heart, on the other hand, there would not be the same danger; for the heart could still respond to calls made on it, though its arterial blood would always be deficiently saturated with oxygen, owing to the admixture of a certain proportion of venous blood. It is even possible that the carbon dioxide threshold of the mixed arterial blood in such a case might be normal during rest, though that of the alveolar air is lowered. Increased rate of circulation or increased percentage of hæmoglobin might, perhaps, compensate for the deficient oxygenation of the mixed arterial blood.

The administration of oxygen in cases of obstructed circulation will increase the oxygen in the arterial blood very appreciably—partly by producing complete saturation of the hæmoglobin, and partly by greatly increasing the small proportion of free oxygen carried in simple solution. In these two ways an increase of about a sixth in the oxygen carried may probably be produced. The whole of this extra oxygen is, however, very readily available, since it is at a very high partial pressure, so that for all practical purposes the increase might be reckoned at about a third. The effect may therefore be, and often is, very striking. Cyanosis may disappear, and considerable relief may result, so that a patient is tided over some bad attack. The oxygen must, however, be given nearly pure,

or at any rate in considerable concentration, in order to produce the full effect. A mouthpiece and tube, or a mask, is therefore needed; and unless the oxygen is used very wastefully, there must be an arrangement for absorbing the carbon dioxide so as to enable the same oxygen to be breathed again and again. A small quantity of oxygen, which can, if necessary, be generated on the spot from oxylithe, will thus suffice for a considerable time. Continuous breathing of pure oxygen over a long period is probably not advisable, on account of its gradual irritant effect on the lungs. If the lungs are œdematous, the addition of even a small proportion of oxygen to the inspired air may, perhaps, have a great effect, as will be explained below in connection with Lung Affections.

The manner in which the body may adapt itself to an impaired general circulation is of great interest, but does not seem to have been very fully studied hitherto, except, perhaps, as regards hypertrophy of the heart. One important adaptation seems to be increase in the percentage of hæmoglobin, so that the oxygen-carrying power of the blood is increased. To judge from measurements by Lorrain Smith, and by Douglas and the writer, the total blood-volume is also increased; and possibly this signifies, not merely an increase of the blood and blood-pressure in the venous system, but an increase in the number of capillaries, so that the blood is brought nearer to the living tissues which it has to supply. There are various other possible adaptations, such as diminution in the peripheral resistance to blood-flow, increased activity of oxygen absorption by the lungs, modification of the dissociation curve of the oxyhæmoglobin of the red corpuscles, increase in the number of capillaries or in the power of their endothelial walls to regulate exchange of material between the blood and tissues, and economy in the distribution of blood to parts which do not require a large blood-supply. On such points we know nothing as yet; nor shall we know much until experimental pathology is studied in the confident faith that the body is a living organism, and not a mere piece of mechanism. The fact that one sees people going about and following their ordinary occupation with their lips blue from cyanosis certainly suggests that, in relation to defective circulation the body possesses means of adaptation which are not yet understood, and the study of which might greatly help in rational treatment.

**Interference with the Oxygen-carrying Power of the Blood.**—While practically nothing is known as yet as to any conditions in which the power of the blood in carrying carbon dioxide is seriously interfered with, various conditions are known in which its oxygen-carrying power is impaired. Part of the hæmoglobin may be rendered useless by poisons which abolish its oxygen-carrying power, such as carbon monoxide or nitrites, or the hæmoglobin may be present in diminished proportion, as in anæmia.

**Carbon Monoxide Poisoning.**—Poisoning by carbon monoxide is of considerable practical interest, as it occurs not infrequently from escapes of lighting gas,* accidental fires, the use of certain kinds of flueless stoves, and various other causes. It is the cause of nearly all the deaths in the great colliery disasters from explosions or underground fires.† In America it is extremely common on account of the general use of undiluted carburetted water-gas for domestic lighting purposes.

It was discovered by Claude Bernard that carbon monoxide has the property of displacing the oxygen of oxyhæmoglobin by forming a more stable compound, carboxyhæmoglobin, and thus depriving the blood of its oxygen-carrying power. To this property it owes its action as a poison. It has often been supposed to act in other ways than by cutting off the oxygen-supply to the tissues. That it does not do so is proved by the fact that, as shown by the writer,‡ its action is abolished in presence of oxygen at two atmospheres' pressure, since the animal experimented on obtains enough of oxygen in free solution in the blood to support life. The hæmoglobin is completely saturated with carbon monoxide in this experiment, as can easily be shown by killing the animal *in situ* and examining its blood colorimetrically. Insects, which have no hæmoglobin, can live for weeks in an atmosphere containing 80 per cent. of carbon monoxide and 20 per cent. of oxygen. Carbon monoxide thus behaves as a physiologically indifferent gas, apart from its one fatal property of uniting with hæmoglobin. The only known respect in which it seems to have some slight direct physiological action is in its effect on the olfactory nerves. It has a slight but very distinct garlic-like odour, although for some unknown reason it is almost always described as an "odourless" gas.

Like oxyhæmoglobin, carboxyhæmoglobin is a compound which dissociates when exposed to a vacuum. In the absence of oxygen, however, it is practically almost impossible to remove the whole of the carbon monoxide from carboxyhæmoglobin by means of the blood-pump. In presence of oxygen the dissociation occurs far more readily, as the mass action of the oxygen drives out the carbon monoxide. Hence, in presence of a mixture of carbon monoxide and oxygen, hæmoglobin becomes partly saturated with carbon monoxide, and partly with oxygen. In accordance with the ordinary law of mass action, the proportion in which the hæmoglobin shares itself between the two gases varies with their relative partial pressures. Hence, if we know the degrees of relative saturation which correspond to any two relative partial pressures,

* See *Report of the Water-Gas Committee*, Parliamentary Paper (C. 9164), 1899.

† Haldane, *Report on the Causes of Death in Colliery Explosions*, Parliamentary Paper (C. 8112), 1896; new edition, 1910.

‡ *Journ. of Physiol.*, xviii. 201, 1895; *ibid.*, xxi. 160, 1897.

we know what degrees of relative saturation will correspond to any two other partial pressures. To take an example: in the case of undiluted human blood at body temperature, the hæmoglobin becomes about half saturated with carbon monoxide, and half saturated with oxygen, in presence of a mixture of about 0·07 per cent. of carbon monoxide with pure air. Hence, with double as much carbon monoxide the blood becomes two-thirds saturated with carbon monoxide in presence of air; or with the oxygen in the air reduced to half its normal percentage, exactly the same result follows. This law has been verified outside the body by numerous experiments with blood or hæmoglobin solutions. It is thus evident that, if we know the final percentage saturation of the hæmoglobin in blood exposed to a given partial pressure of carbon monoxide and an unknown partial pressure of oxygen, we can at once infer the partial pressure of the oxygen, provided that we already know how the blood behaves in presence of any two known partial pressures of the two gases.

This is the principle of the method employed by Lorrain Smith, Douglas, and the writer, for determining the partial pressure of oxygen in the arterial blood leaving the lungs.* The animal is given a known small percentage of carbon monoxide to breathe. After a sufficient time has elapsed, the blood ceases to take up any more carbon monoxide. The percentage saturation of the hæmoglobin with carbon monoxide is then determined colorimetrically in a drop of the blood diluted with water in the manner described below. Some of the blood is also exposed to saturation at body temperature to a known percentage of carbon monoxide in air (the same, if possible, as what the animal has breathed), so as to obtain the constant required in the calculation. The partial pressure of the oxygen in the arterial blood can then be deduced at once. The results obtained by this method have already been alluded to above. For experiments on men the method is modified, but the principle is the same.

The colorimetric determination of the percentage saturation with carbon monoxide depends upon the following principles: Blood saturated with carbon monoxide possesses, on dilution in a test-tube to about $\frac{1}{150}$ or more, a very characteristic pink colour, which contrasts strikingly with the yellow of oxyhæmoglobin similarly diluted. This fact affords a ready test, far exceeding any other in delicacy and certainty, for the presence of carbon monoxide in blood. The degree of pinkness as compared with yellowness is of course proportional to the percentage saturation with carbon monoxide. By adding carmine solution to the solution of normal blood, it is possible to bring it to exactly the same degree of pinkness as that of the abnormal blood-solution or of blood-solution fully saturated with carbon monoxide. This affords a means of

* *Journ. of Physiol.*, xliv. 305, 1912.

estimating quantitatively the percentage saturation of the hæmoglobin with carbon monoxide, and the results obtained are extraordinarily exact when the proper precautions are taken. By the same method the percentage saturation of the blood in cases of carbon monoxide poisoning can be ascertained. As oxygen is absent after death, and both hæmoglobin itself and carboxyhæmoglobin are exceedingly stable in the absence of oxygen, the percentage saturation can still be determined long after putrefaction has set in. Any sample must, however, be protected from the oxygen of the air until the determination is made.

The symptoms of carbon monoxide poisoning* are essentially those of want of oxygen, already described, and depend on the gradual curtailment of the oxygen-supply to the tissues in proportion as the hæmoglobin becomes more and more saturated with the carbon monoxide. As this saturation increases, as a rule, very gradually, there is no noticeable air-hunger or hyperpnœa to give warning of the danger. The saturation creeps up and up; mental power becomes gradually but unconsciously impaired; and finally the power of voluntary movement and perception is lost, and a state of deep coma supervenes, which ends in death if the saturation increases much further. Clearly, however, the increase in saturation will stop as soon as the partial pressure of oxygen in the arterial blood balances the partial pressure of carbon monoxide. With small percentages of carbon monoxide in the air, this stage may be reached at a point corresponding to anything between no symptoms at all and the deepest coma short of actual death. The corresponding range in the percentages of carbon monoxide in the air is very considerable—up, probably, to about 0·5 per cent. of carbon monoxide in the case of man, but varying with different individuals and under different circumstances. At death the percentage saturation of the blood is usually about 80 to 85 per cent., in the writer's experience of human cases; and in animals much the same result is found. Sometimes, however, death occurs at as low as 60 per cent. saturation, either with animals or men.

The percentage saturation of the blood cannot be accurately inferred from the percentage of carbon monoxide in the air; for, as already mentioned, the influence of the layer of living cells between the alveolar air and the blood entirely alters the dissociation curve obtained in experiments with blood outside the body. With low percentages of carbon monoxide the percentage saturation in the blood of an animal is greater than in the blood exposed to air, indicating that the partial pressure of oxygen is practically that of the alveolar air. With high percentages of carbon monoxide, on the other hand, the relation is reversed, showing that the oxygen pressure in the arterial blood is above that in the alveolar air, and even considerably above that in the inspired air. The want of

* Haldane, *Journ. of Physiol.*, xviii. 430, 1895.

oxygen produced by the high percentages excites the secretory activity of the lungs.

In different animals, and to some extent in different individuals of the same species, the dissociation curve of oxyhæmoglobin varies, as we have already seen. A similar variation is found in the dissociation curve of carboxy-hæmoglobin in presence of air and carbon monoxide, and this fact introduces a further complication.

If the percentage of carbon monoxide is high, exceeding about 1 per cent., the symptoms produced pass into those of fairly rapid deprivation of oxygen. Thus, the hyperpnœa is more marked, owing to the more rapid lowering of the carbon dioxide threshold, and consequent necessity for rapid removal of preformed carbon dioxide from the body. Death may then be preceded by convulsions and accompanied by signs of great venous engorgement, as in other cases of rapid death from want of oxygen. With still higher percentages, death occurs before the whole of the blood has had time to saturate itself at all uniformly. The blood on the right and left sides of the heart may thus be quite differently saturated, and hardly any carbon monoxide may be found, for instance, in the blood of the spleen. After colliery explosions the saturation of the blood of the men who have been killed is uniform all over the body, and usually very high, and it is exceptional to find cases where there is venous engorgement indicative of pretty rapid death. Whether or not the men have been burnt or injured by the explosion (and usually they are neither burnt nor mechanically injured), they must have died quite slowly in an atmosphere containing enough of oxygen to support life, with only a small percentage of carbon monoxide. It would thus be possible to save many of them if fresh air could be got in without much delay, or if they could be brought out or effectually protected from carbon monoxide in any other way.

The symptoms produced by gradual saturation of the blood from carbon monoxide can hardly be elicited in any ready way until the blood is about a fourth saturated. It will then be found that any considerable exertion begins to produce unusual hyperpnœa, with slight dizziness and unusual palpitation within about a minute. As the saturation increases, these symptoms become more and more easy to elicit, so that they readily attract attention with the blood a third saturated. Evidently the heart cannot properly respond to the exertion, and the blood-pressure falls, producing the dizziness, while the unusual hyperpnœa is mainly due to rapid formation of lactic acid in the active muscles. With further increase in the saturation, an indefinite sense of abnormality begins to be noticed during rest, along with slight palpitation or throbbing of arteries, and the dizziness on exertion becomes more and more marked. The breathing is doubtless also somewhat increased in depth, but this symptom is not appreciable subjectively. At about 50 per

cent. saturation it is barely possible to walk any distance, even in a room, and the smallest extra exertion causes collapse on the floor. At 56 per cent. saturation the writer found it impossible to rise from his seat without collapsing on the floor. There was, however, no discomfort or air-hunger, but apparently some exhilaration, interest in the experiment being still quite keen, though somewhat confused, there being various objective signs of mental disturbance. The idea of seeing the experiment through seemed to be a " fixed " one, and this kind of fixation of ideas, regardless of either danger or anything else, appears to be characteristic of gradually progressive want of oxygen, and probably accounts largely for the great dangers of high balloon ascents or of venturing far into after-damp in rescue operations after a colliery explosion. The person himself is always absolutely convinced at the time that his head is quite clear, and that he is acting quite rationally, and even prudently.

When the saturation exceeds about 50 per cent., there appears to be much danger from any considerable exertion. For instance, it may often be observed that an animal which begins for any reason to struggle will suddenly collapse, go into convulsions, and die. Men also seem often to die as an immediate consequence of too sudden efforts, as in trying to ascend ladders or steep inclines in a mine. If convulsions follow on fainting, there seems little chance of a further and fatal fall of blood-pressure being averted, unless artificial respiration is applied.

Anything exceeding about 0·02 per cent. of carbon monoxide in air will, in time, produce symptoms of carbon monoxide poisoning. With less than about 0·02 per cent., however, the balancing-point at which absorption ceases is reached before the saturation of the blood is sufficient to produce distinct symptoms. As only about half the carbon monoxide is absorbed even at first, and as the proportion absorbed falls off rapidly in proportion as the balancing-point is approached, it takes many hours in man for this point to be reached with so small a proportion of the gas in the inspired air. As the percentage breathed increases, however, the time becomes less and less, as follows from the form of the dissociation curve and the characteristic distortion of this curve in the living animal. Even with a considerable percentage in the air, however, the latent interval before any symptoms are produced is so long as to cause great danger from men venturing too far into a poisonous atmosphere in mines. As much as about 0·4 per cent. can, for instance, be breathed for half an hour during rest before sudden disablement is produced. During muscular exertion, however, the rate of absorption is greatly increased.

The presence of a dangerous percentage of carbon monoxide in air can be easily and safely detected by means of a small warm-blooded animal, such as a mouse or small bird.* In these animals

* Haldane, *Journ. of Physiol.*, xviii. 448, 1895.

the metabolism per unit of weight is, of course, enormously greater than that of a man. They consequently react to carbon monoxide in a mere fraction of the time needed to affect a man, and consequently the small animal can be safely used as an indicator of carbon monoxide by a man carrying it. A bird in a cage is a somewhat more delicate test than a mouse, as the point at which the bird can no longer sit steadily on its perch is easily seen, and it usually dies with a lower percentage of the gas. When the percentage of carbon monoxide is too small to cause symptoms, the presence of the gas can still be readily detected by killing a mouse which has been left for a few minutes in the poisonous atmosphere, and examining its blood for carboxyhæmoglobin by the colour test.

Desaturation of the blood by elimination of the gas through the lungs occurs fairly fast when pure air is breathed. The process is of course rapid at first, and tails off as the saturation of the blood diminishes. About three hours may suffice for practical completion of the process, though the time will vary according to the amount of air breathed. It is a common mistake to suppose that the time required is very long, or even that the blood-corpuscles never recover. There is no evidence whatever that they are permanently injured in any way. Carbon monoxide is not oxidized or otherwise attacked within the living body. It behaves as a purely indifferent gas, apart from its action on hæmoglobin ; and it leaves the body by the lungs, just as it enters by the lungs.

If oxygen is administered in a case of carbon monoxide poisoning, the rate at which the carbon monoxide is eliminated is, of course, greatly accelerated, as the increased partial pressure of oxygen in the blood passing through the lungs will, of course, drive out the carbon monoxide about six times as fast as if air is breathed. Still more effective in this respect would be a mixture of oxygen with about 4 or 5 per cent. of carbon dioxide. This would stimulate the breathing and circulation, and thus hasten the process. An equally important action of oxygen is that it at once furnishes a sufficient supply of oxygen to the tissues ; for the amount in pure solution, along with that carried by the hæmoglobin which is still available as an oxygen-carrier, is quite sufficient to restore consciousness at once, in so far as it can be restored at once by re-establishing the oxygen-supply to the brain. Addition of carbon dioxide also increases this action by stimulating the circulation. This latter action is very striking in animals. An animal which is practically comatose from carbon monoxide can be waked up at once by adding carbon dioxide to the poisonous air. Whether or not oxygen can be obtained for the treatment of carbon monoxide poisoning, no time should be wasted over sending for it. Prompt removal to fresh air, and artificial respiration by Schäfer's method, if necessary, are the first requisites. The importance of avoiding exposure to cold, or any muscular exertion before complete recovery, have already

been alluded to. Continued administration of oxygen after the first half-hour would seem to be useless. It should also be remembered that excessive artificial respiration may easily produce apnœa, followed by Cheyne-Stokes breathing.

**Methæmoglobin-forming Poisons.**—A considerable number of poisonous substances, many of which are used as drugs, possess the property of converting hæmoglobin into either methæmoglobin or other derivatives of the hæmoglobin molecule, thus diminishing the oxygen-carrying power of the blood for the time. If the process goes beyond the stage of methæmoglobin, the result is the more serious, as the hæmoglobin cannot recover, and anæmia lasting for some time is produced.

As a type of the methæmoglobin-forming poisons, any nitrite may be taken as an example, although nitrites form from oxyhæmoglobin not merely methæmoglobin, but also a certain proportion of nitric-oxide-hæmoglobin, to the presence of which is due the reddish colour and peculiar spectrum of the product, as compared with the dull brown of pure methæmoglobin. As a type of the poisons which produce a further and more destructive action on the hæmoglobin, dinitrobenzol (a substance used a good deal in manufacturing processes, and present in some explosives) may be instanced.

The serious nature of the blood-changes produced by these substances was first suspected from post-mortem examination of persons who had died after treatment with chlorate of potash in considerable quantities for diphtheria, etc.; and chlorate of potash is one of the drugs which produce the changes in question.

Except, perhaps, sodium chlorate, nearly all the substances belonging to the group in question have a poisonous action apart from their influence in cutting off the oxygen-supply, and the question arises, to what extent their poisonous action is due to their action in cutting off the oxygen-supply. This question was tested for several members of the group by ascertaining whether, when placed in compressed oxygen in the manner already described in connection with carbon monoxide, the animals survived after a dose which would otherwise be fatal. Sodium and amyl nitrite, and dinitrobenzol were tested in this way, and it was found that the animals survived in the oxygen, while they died rapidly in convulsions if removed to air. There could thus be no doubt that these poisons actually prove fatal, just as carbon monoxide does, by producing asphyxia from want of oxygen. The degree to which the hæmoglobin was thrown out of action was also measured, and the symptoms were found to correspond pretty closely to those of carbon monoxide poisoning at similar stages.*

Another important fact ascertained was that, if an animal was tided over the worst period by keeping it in the oxygen for a short time, the blood rapidly became normal again, and the animal could

* Haldane, Makgill, and Mavrogordato, *Journ. of Physiol.*, xxi. 160, 1897.

safely be returned to ordinary air. Oxygen at ordinary pressure was quite effective in this respect, as the whole of the hæmoglobin was never altered. There remained enough of oxyhæmoglobin to maintain a sufficient oxygen-supply to the tissues, provided that this supply was supplemented by the dissolved oxygen resulting from the respiration of pure oxygen. Cases of poisoning by this group of poisons can thus be effectively treated by oxygen.

The conversion of methæmoglobin back again into oxyhæmoglobin in the living body is an interesting fact, pointing to the presence of a so-called "reducing substance" within the red corpuscles. In presence of a reducing substance (such, for instance, as ammonium sulphide), methæmoglobin is instantly reduced to hæmoglobin; and if, as in ordinary test-tube experiments, free oxygen is also present, the hæmoglobin is at once converted into oxyhæmoglobin. In nitrite-poisoning it is evident that there is, as it were, a constant struggle within the corpuscles between the two processes of production of methæmoglobin by the influence of the nitrite and reconversion back by the "reducing substance." The dose of nitrite may be pushed to extremes, but there is always some oxyhæmoglobin left; and if death does not occur, the reconversion process soon gets the upper hand, as the nitrite is gradually destroyed or eliminated.

The first symptom of poisoning by one of the members of this group is (apart from any symptoms due to other actions of the poison) an appearance of cyanosis. The lips, etc., become of a most alarming colour, often before the person feels otherwise ill. The colour is, of course, due to methæmoglobin, and has not in reality the same alarming significance that would attach to the presence of reduced hæmoglobin, as in true cyanosis; for the partial pressure of oxygen is still normal, or nearly so, in the circulating blood. In slight cases there may be practically no symptoms at all except the apparent cyanosis. On examining the blood with the Gowers-Haldane hæmoglobinometer, it will be found that it is impossible to match the tint of the standard by saturating the solution of the patient's blood with carbon monoxide or coal-gas. The methæmoglobin or other pigment present makes the patient's blood yellower, and the hæmoglobinometer reading would be worthless as a measure of the oxygen-carrying power of the blood. On the other hand, the peculiar tint of the patient's blood after saturation with coal-gas draws attention at once to the real state of matters. Spectroscopic examination is also useful, but in the case, for instance, of dinitrobenzol-poisoning nothing giving a distinct absorption band may be present in the blood, although it is coffee-coloured from the presence of abnormal pigment.

In cases where serious anæmia is produced by the blood-destruction in acute or chronic poisoning by such substances as dinitrobenzol or anilin, and where death is threatened if treatment by oxygen is discontinued, transfusion of human blood should be

resorted to. New red corpuscles would, it is true, be formed in time; but the time required is considerable, and meanwhile the patient may die of pneumonia from the continued action of the oxygen on the lungs, if not from want of oxygen in the tissues.

After death from nitrite-poisoning, the whole of the hæmoglobin becomes converted into nitric-oxide-hæmoglobin, just as occurs in the process of salting meat when nitre is added to the salt. The body is red, and the blood has the characteristic double-banded spectrum, which might easily be mistaken for that of carboxy-hæmoglobin.

**Anæmias.**—The distinctive feature of all so-called "anæmia" is that the *percentage* of hæmoglobin in the blood is abnormally low. As the percentage of hæmoglobin is practically an exact measure of the oxygen-carrying power of the blood, anæmias have this in common with carbon monoxide poisoning, that the normal oxygen-carrying power of the blood is lowered. We might therefore expect that in anæmias symptoms of want of oxygen similar to those observed in carbon monoxide poisoning would be met with. Nothing is more striking, however, than the contrast between a woman suffering from chlorosis, or a man from ankylostomiasis, with the blood reduced to 30 per cent. of its normal oxygen-carrying power, and a person suffering from carbon monoxide poisoning with a similar reduction in the oxygen-carrying power. The anæmic person is probably going about much as usual: the anæmic house-maid is doing her work, and the anæmic miner is doing his work—with difficulty in each case, it is true; but the person suffering from carbon monoxide poisoning is comatose and at the point of death.

The alveolar air during rest has been examined by FitzGerald* in a large number of cases of chlorosis and other anæmias, and has been found to be practically normal. There is thus no fall in the carbon dioxide threshold, such as seems invariably to indicate the existence of shortage of oxygen. In other words, the respiration is perfectly normal during rest. As we have seen, the blood ordinarily loses about a third of its oxygen during the systemic circulation; but if the same rate of oxygen loss and of blood-flow were maintained in anæmia, with the oxygen-carrying power of the blood reduced to a third of the normal, there would be no oxygen at all left in the venous blood, and there would also be intense cyanosis, of which not a trace can be actually seen. It is evident, therefore, that the circulation is greatly accelerated, and that there is a general dilatation, or possibly multiplication, of arterioles in order to permit of this. It is possible that there may be a similar increase in circulation rate during carbon monoxide poisoning; but in the latter case the dissociation curve of the remaining oxyhæmoglobin is so altered as to increase greatly the symptoms of want of oxygen.†

* *Journ. of Pathol.*, xiv. 328, 1910.

† J. B. S. Haldane, *Journ. of Physiol.*, xlv.; *Proc. of Physiol. Soc.*, Oct. 1912.

As was shown by Lorrain Smith, the blood-volume is greatly increased in chlorosis, while the total quantity of hæmoglobin in the body is normal; and the same is true of ankylostomiasis, and probably of anæmias secondary to other illnesses. Even in anæmias resulting from bleeding, and in pernicious anæmia, where the total hæmoglobin is diminished, the blood-volume seems to be commonly increased. Many of the facts suggest that the "anæmia," or rather hydræmia, is secondary to a loss of vascular tonus, with consequent increased capacity of the bloodvessels and increased flow of blood through them with a given arterial pressure; but however this may be, the absence of symptoms of shortage of oxygen during rest necessitates the assumption of increased rate of blood-flow.

In all anæmias muscular exertion produces unusual breathlessness. The exact cause of this has not yet been definitely ascertained, but it seems probable that it is due mainly to rapid formation of lactic acid in the muscles, and discharge of this into the blood, with consequent temporary lowering of the carbon dioxide threshold, necessitating a great and rapid discharge of preformed carbon dioxide from the body. There seems to be a marked contrast between the breathlessness on exertion of an anæmic patient, and the faintness (accompanied by breathlessness, however) produced by exertion in carbon monoxide poisoning. The latter is certainly due mainly to heart failure. The former has all the appearance of being due mainly to carbon dioxide. It certainly seems as if, possibly because the arteries are already more or less relaxed, the circulation through the muscles could not sufficiently respond to muscular exertion in anæmia, with the result that local want of oxygen in the muscles and formation of lactic acid occurs very rapidly. The extra breathlessness would thus only be similar in nature to what immediately follows some excessive exertion in a normal person. Here the initial breathlessness is out of proportion to the increased exertion, owing to rapid liberation of lactic acid and consequent lowering of the carbon dioxide threshold, as has already been explained in connection with normal respiration.

It seems to be only in extreme cases of ordinary chronic anæmias that heart failure is prominently associated with muscular exertion, as in carbon monoxide poisoning. In cases of anæmia rapidly produced by hæmorrhage, however, we have probably a condition resembling carbon monoxide poisoning in many ways. Sudden loss of as much as half the blood is very dangerous to animals, even if liquid is injected to make up for the volume taken away. The circulation does not seem to adapt itself in time to the reduced oxygen-carrying power of the blood. In the treatment of such cases in man, the administration of pure oxygen might prove very useful where transfusion of human blood cannot be performed at once. On the other hand, there is no clear evidence as yet that the dangers of sudden hæmorrhages are dependent on want of oxygen.

**Polycythæmia.**—In spleno-megalic polycythæmia both the percentage of hæmoglobin and the total blood-volume are greatly increased. If, therefore, the polycythæmia were a primary condition, we might expect the oxygen-supply to the tissues to be abnormally increased. As a matter of fact, however, cyanosis is associated with the polycythæmia, so that the rate of blood-circulation must be diminished, leading to some actual shortage of oxygen; and possibly the polycythæmia is a compensatory change, as in congenital and other heart cases, or persons living at great altitudes. In a case examined by FitzGerald, the alveolar carbon dioxide percentage was a good deal below the normal average; and this also points towards some shortage in the oxygen-supply.

**Interference with Gaseous Exchange in the Lungs.**—From the account given above of the conditions determining gaseous exchange between the alveolar air and the blood, it seems evident that this exchange may easily be interfered with seriously under pathological conditions. Unfortunately, however, our knowledge on this subject is very meagre, clinical or experimental data of an intelligible kind being as yet unavailable.

Any cause, such as exudation or inflammatory thickening, which increases the distance between the alveolar air and the blood must hinder exchange of gases by diffusion, since it will diminish the steepness of the gradient of difference in gaseous partial pressure in the substance separating the air and the blood. Moreover, any unhealthy condition affecting the lung will probably weaken or entirely paralyze active secretory absorption or excretion of gas by the cells in the alveolar wall. It seems almost certain that absorption of oxygen will be the first thing to suffer seriously under such conditions; for, owing to the low solubility of oxygen, its transference by diffusion will be much more readily hindered than that of carbon dioxide. The transference of carbon dioxide by diffusion can, moreover, be enormously facilitated by an increase in the breathing which would hardly be appreciated subjectively. Thus, doubling the depth of breathing would apparently multiply by several times the mean difference in partial pressure of carbon dioxide between the alveolar air and the blood; but no striking advantage would be gained in the case of absorption of oxygen, as the mean difference in oxygen pressure between the alveolar air and the blood in the alveolar capillaries would only be slightly increased. We may thus expect that symptoms of want of oxygen would be readily produced. The dusky appearance, or even extreme cyanosis, often met with in inflammatory or œdematous conditions of the lung certainly also suggests that this is the case.

It would be wrong to conclude straight away from the existence of cyanosis (and particularly of the leaden colour of the lips which seems characteristic of cyanosis due, not to blockage in the circulation, but to deficient oxygenation of the arterial blood), that in

pulmonary affections oxygen absorption is interfered with in the particular manner just indicated. For bronchioles may be more or less blocked mechanically, and blood may be passing in considerable quantity to the left side of the heart from parts of the lung which are entirely blocked by exudation or in consequence of collapse. Either of these causes would also produce cyanosis along with, probably, only slight air-hunger, as the carbon dioxide in the arterial blood could easily be kept down. That there may, however, be a great drop in the oxygen pressure of the arterialized blood leaving the alveoli which are still open seems to be conclusively proved by Lorrain Smith's determinations by the carbon monoxide method in the case of incipient pneumonia produced by the respiration of oxygen at a high partial pressure.

Apart from blocking of bronchioles or interference with gaseous exchange through thickening of the alveolar walls, gaseous exchange may be interfered with by imperfect distribution of air in the various parts of the lung. Cyanosis is often an extremely marked symptom in emphysema of the lungs. The most natural explanation of this would seem to be that the normal distribution of air over the lung alveoli has broken down, too much air probably going to the distended and more or less bloodless and atrophied parts, while too little goes to other parts. The over-ventilation of some parts will compensate more or less for the under-ventilation of others as regards carbon dioxide, so that the carbon dioxide pressure in the mixed arterial blood may be normal or below normal; but there can be no appreciable compensation with regard to oxygen. The consequence will thus be that cyanosis will be produced, unaccompanied, perhaps, by subjectively appreciable shortness of breath except on exertion. On the other hand, the cyanosis may be due to slowing of the circulation from increased resistance to blood-flow through the lungs.

Beddard and Pembrey* record a case in which striking effects were produced by giving oxygen in a case of capillary bronchitis accompanied by cyanosis. The cyanosis disappeared, and the lung ventilation was reduced to half. There were no signs of circulatory failure in this case, so that the cyanosis was clearly due to the local condition in the lungs.

In cases where the want of oxygen is caused simply by the difficulty in getting a sufficient supply of oxygen through alveolar walls which are thickened or clogged by exudation or imperfectly supplied with oxygen, striking improvement would certainly be produced by the administration of air containing only a slightly increased proportion of oxygen; and this treatment could safely be continued for many days if necessary. Clinical accounts of marked improvement where oxygen has been given in small amounts through a funnel held near the patient's nose seem to confirm this inference; but more reliable observations are much needed.

* *Brit. Med. Journ.*, ii. 581, 1908.

**Interference with the Respiratory Centre.**—Apart from any serious interference with the general conveyance of gases between the tissues and the lungs, the respiratory centre itself may be affected in different ways. Thus, substances may be present in the blood which either excite or depress its normal activity; or the circulation in the centre may be interfered with locally, thus causing want of oxygen or excess of carbon dioxide to act upon it specially.

Of substances in the blood which abnormally excite the respiratory centre, the best known are acids. In general poisoning by an acid the breathing becomes very abnormally deep, so that the alveolar carbon dioxide is doubtless reduced to a fraction of its normal amount, while the percentage of carbon dioxide in the arterial blood itself is also reduced to a minimum, as little as 5 per cent. by volume having been found by Walter* in an extreme case. This latter reduction seems to be mainly due to the greatly increased washing out of carbon dioxide, by the lung ventilation, rather than to any great diminution in the power of the blood to carry carbon dioxide in chemical combination.† In diabetic coma, where there is a great accumulation of oxybutyric acid in the blood, the respiratory phenomena are evidently also due to the acid poisoning, and Beddard, Pembrey, and Spriggs, have found as little as 1·2 per cent. of carbon dioxide in the alveolar air, and that the proportion increases as the patient improves. Dilute solutions of caustic alkalies injected into the carotid artery produce temporary apnœa, as might be expected. Curiously enough, however, bicarbonates if similarly injected excite the centre, the carbon dioxide being evidently liberated in the blood. As to other substances which, when present in the blood during disease or otherwise, directly excite the respiratory centre, our knowledge is very defective.

A number of poisons are known which paralyze the respiratory centre before they produce death otherwise. Of special interest, perhaps, is the direct action of chloroform and other anæsthetic or narcotic substances. It appears that some, at least, of these drugs may raise the carbon dioxide threshold to such an extent as to produce temporary apnœa or very shallow breathing, during which the alveolar oxygen percentage runs down to such an extent as to make the arterial blood extremely venous, and thus cause immediate danger of asphyxia from want of oxygen. A sudden raising of the carbon dioxide threshold must certainly tend to produce this effect, as the oxygen pressure in the alveolar air and blood runs down far faster than the carbon dioxide pressure rises. This point has already been referred to in connection with the phenomena of apnœa under normal conditions. From Yandell Henderson's experiments, it would seem that a sufficiently sudden and considerable rise in the carbon dioxide threshold would

* *Archiv f. Exper. Pathol.*, vii. 148, 1877.

† Loewy and Münzer, *Archiv f.* (*Anat. u.*) *Physiol.*, 81, 1901.

inevitably cause asphyxia unless artificial respiration were reverted to. In animals deeply under chloral, morphia, etc., the arterial blood may be quite dark in colour, and this suggests that the carbon dioxide threshold is raised to such an extent as to entail a very low coincident pressure of oxygen in the alveolar air, even while the breathing is quite regular.

Want of oxygen itself is, of course, one of the causes which produce paralysis of the respiratory centre some time before the heart stops or irreparable injury is produced in the central nervous system; and continuous shortage of oxygen produces, in all probability, a state of depressed excitability in the centre. Pembrey and Allen found, on investigating a case where, from the presence of Cheyne-Stokes breathing and other evidence, there was certainly shortage in the oxygen-supply to the respiratory centre, that a condition of very abnormal tolerance of excess of carbon dioxide existed.

When the circulation to the respiratory centre is impaired, there must occur locally both a rise in carbon dioxide pressure and a fall in oxygen pressure. It might at first be supposed that the rise would about equal the fall, just as occurs when the breathing is mechanically hindered, and that, as the centre is so extremely sensitive to rise in carbon dioxide pressure, the effects of carbon dioxide would predominate. A little consideration will show, however, that this will not be the result. Let us suppose that there is a sudden impairment of the circulation. The pressure of carbon dioxide will rise only slowly, as the storage capacity of the tissues and blood for carbon dioxide is large. On the other hand, the oxygen pressure will fall very rapidly, as the blood cannot yield its oxygen without a great fall in the oxygen pressure, and the storage capacity of the blood for oxygen is small. The effects of want of oxygen will thus predominate, in complete contrast to what happens when the breathing is mechanically impeded. Let us now suppose that the impaired circulation is continued. The centre will be excited by the effects of want of oxygen (lactic acid) and carbon dioxide combined. In consequence the breathing will be increased, and the arterial blood will contain much less carbon dioxide, but practically no more oxygen. This blood will reach the centre and relieve the dyspnœa, considerably at least, by lowering the pressure of carbon dioxide in it; but the lack of oxygen will remain. If the centre continues to act at all, its excitation will be dependent mainly on the lack of oxygen; but probably its nutrition will become impaired and it will lose much of its sensibility. Since, moreover, it is responding mainly to want of oxygen, it will be abnormally sensitive to changes in the oxygen-supply, brought about by small variations in the circulation, just as we saw to be the case when the experimental production of Cheyne-Stokes breathing was discussed above. The centre will thus probably begin to act in a periodic manner, just as a sensitive governor of an engine without

a flywheel begins to "hunt"; for any increase in the respirations will produce some increase in the circulation, and the consequent rapid quieting effect on the respiratory centre will in its turn diminish or abolish the respirations; and so the process will tend to go on continuously, just as it does, though with a different period of rhythm, in a person sleeping at a high altitude, or in the case of one or other of the different ways in which Cheyne-Stokes breathing may be produced experimentally in a normal person.

That ordinary clinical Cheyne-Stokes breathing is dependent on want of oxygen was first shown experimentally by Pembrey and Allen,* who found that it is abolished by giving oxygen, and also, as might be expected, by either air containing an excess of carbon dioxide or deficient in oxygen. It appears to be specially associated with conditions in which the cerebral circulation in particular is impaired; but apparently any condition in which the centre is acted upon by slight want of oxygen may give rise to it, whether the want of oxygen depends on the condition of the alveolar air or on defective circulation. It is thus a common symptom of failing circulation or respiration, but may also appear under conditions of perfect health, if the required conditions are in any way produced. In the cases in which the alveolar air was investigated by Pembrey, it appeared that the average lung ventilation was abnormally increased, and the carbon dioxide percentage very low in the alveolar air. This fact points very clearly to defective circulation as the cause of the Cheyne-Stokes breathing; and the defective circulation appeared from other evidence to be in the brain. Cheyne-Stokes or periodic breathing is occasionally observed in healthy persons during sleep, when air at ordinary pressure is breathed. This, and the varying susceptibility of the respiratory centres of different persons to deficiency of oxygen in the air, seems to suggest that in some persons the circulation through the respiratory centre under normal conditions is only just sufficient to prevent the centre from being affected by want of oxygen, so that any slight diminution in the circulation, as during sleep, may cause periodic breathing. In other persons, with perhaps an extra good circulation through the centre, air which is deficient in oxygen causes no respiratory response, or very little, before consciousness is lost. In pathological cases the periods of the Cheyne-Stokes breathing, when it is present, are much longer, as a rule, than in Cheyne-Stokes breathing produced during health. This is perhaps due to slowing of the circulation and consequent increase in the time taken by the blood in passing from the lungs to the respiratory centre.

**Interference with Nerves connected with Breathing.**—The abnormal excitation, or absence of excitation, of afferent nerves may affect

* *Journ. of Physiol.*, xxxiii., p. xviii, 1905; *Trans. Med.-Chir. Soc. Lond.*, xc. 60, 1907; *Journ. of Pathol.*, xii. 258, 1907.

the breathing in different ways. Thus, inspiration of an irritant gas is at once inhibited by excitation of the afferent nerves of the nose, larynx, and trachea. This effect is observed, for instance, on the attempt to take a breath of air very rich in carbon dioxide. If the irritant atmosphere cannot be avoided, the respiratory centre breaks through the inhibition, but the breathing becomes unusually slow. This effect is very striking in animals, the frequency of breathing being greatly diminished, though the depth appears to be increased, if an irritant proportion of any such gas as sulphuretted hydrogen, sulphurous acid, etc., is breathed. Men going into such atmospheres find respiration "difficult." There seems no reason for supposing, however, that the carbon dioxide threshold is materially raised.

The function in breathing of the afferent pulmonary branches of the vagus nerves has already been alluded to. It is an interesting question whether under pathological conditions the action of these fibres may become abnormal and affect the breathing. The nerve endings may, for instance, become hyperæsthetic in inflammatory conditions such as pneumonia, and possibly this may be the explanation of the remarkable frequency of the breathing. Frequent and at the same time shallow breathing is not characteristic of any normal hyperpnœa in man. If the "Hering-Breuer" effects produced by distention and collapse of the lung were exaggerated, frequent, and at the same time shallow, breathing would result, just as deep and slow breathing results if the vagus nerves are divided. Whether the breathing is abnormally rapid or not, the alveolar carbon dioxide probably remains the same, just as it does in a normal individual who, without forcing the breathing, varies its frequency.

The mode of breathing may also be modified by painful afferent stimuli (as in pleurisy, where it becomes shallow and correspondingly frequent), or by emotional or other impulses from higher senses. There is no good evidence, however, for believing that any of these nervous impulses seriously raise the alveolar carbon dioxide threshold. The predominant controlling influence of any rise in the carbon dioxide pressure of the arterial blood seems to break through any disturbance of breathing caused by nervous impulses hindering the action of the respiratory centre. Even the strongest volitional effort is unable to hold back the centre for as much as a minute, although within the period during which the volitional inhibition is possible the alveolar carbon dioxide percentage has only risen by about 1 per cent., and the oxygen percentage fallen by about 4 or 5 per cent. By volitional effort, on the other hand, deliberate forced breathing can be maintained for long periods. Strong nervous stimuli may, as already mentioned, produce a direct effect in increasing rhythmic breathing as measured by its effect on the alveolar carbon dioxide pressure; and the

probability of forced breathing being sometimes temporarily produced in hysterical or other abnormal mental conditions must be borne in mind, together with the very marked physiological phenomena which accompany or follow forced breathing. Forced breathing seems to play a part in the religious exercises met with in some Eastern nations; and, curiously enough, it has also recently come to be introduced as an exercise in courses of "physical training." The possibility of excessive lung ventilation in connection with artificial respiration must also be borne in mind, particularly as Schäfer's method renders artificial respiration very efficient and easy to carry out.

Interference with the ordinary efferent respiratory nerves or nerve endings by severance, pressure of tumours, poisons such as curare, etc., need scarcely, perhaps, be considered here. Much pathological interest attaches, however, to interferences with the normal innervation of the bronchial muscles. As we have seen, Brodie and Dixon have shown that both broncho-constrictor and broncho-dilator fibres pass down the vagus nerve, and that afferent impulses from the nasal mucous membrane are capable of producing reflex broncho-constrictor effects. There are probably other reflex connections by which broncho-constrictor or broncho-dilator effects may be produced; but they have not yet been satisfactorily demonstrated. The one connection known renders to some extent intelligible, however, the influence of certain odorous or irritant substances or of abnormal conditions of the nasal mucous membrane, in the production or alleviation of asthmatic symptoms. It also seems probable that irregular local interference with the bronchial muscles in the lungs may cause not only local disturbances in respiratory exchange between the alveolar air and blood, but serious local distortions of the lung tissue during inspiration or expiration, leading to the occurrence of emphysema.

**Caisson Disease.**—Although caisson disease or compressed air illness does not depend primarily on any special interference with the respiratory processes, its causation and prevention may be conveniently discussed in connection with the subject of respiration. Its occurrence was first observed in connection with the use of special apparatus for deep diving, and of the caissons filled with compressed air which are employed by engineers to enable men to work at the foundations of bridges, etc., under water. Compressed air is now also extensively employed in driving tunnels through soft water-logged strata, where there would otherwise be danger of irruption of water, as beneath rivers; and in such undertakings there is great trouble from caisson disease when the air pressure is considerable.

The symptoms of caisson disease are almost protean; but their common characteristic is that they occur, not in the compressed air, but shortly after return to ordinary atmospheric pressure, or

occasionally even during the return. In the mildest and most common cases there is simply pain, which may be intense, in one or other joint, or elsewhere in the body. These pains pass off in a few hours, and are known to the workmen as "bends," apparently because of the flexed positions which they induce. In other cases there are symptoms of paralysis—usually paraplegia—indicating a localized affection of the central nervous system either in the cord or brain. In other cases there is rapid collapse indicative of interference with the general circulation, and sometimes ending fatally in a few minutes. There may, in fact, be symptoms referable to almost any part of the body, and varying in gravity with the importance of the part affected.

The cause of caisson disease was clearly established by Paul Bert* about thirty years ago by experiments on animals; but the most extraordinary and even wholly impossible theories on the subject are still to some extent current, although every serious investigation, and particularly those of von Schrötter in Austria and Hill† in this country, have confirmed Bert's explanation. Bert showed that in the compressed air the blood takes up nitrogen from the air in simple solution in proportion to the increased partial pressure of this gas. On reducing the pressure rapidly, the nitrogen is apt to be liberated in the form of bubbles, which may block the circulation at any part, or accumulate in the heart and block the general circulation, thus producing the symptoms. Dissolved oxygen is also taken up in increased amount in the arterial blood under the increased pressure, but of course disappears in the systemic capillaries, and thus causes no trouble. From the account given above of the regulation of breathing, it will be seen that there can be no increase in the carbon dioxide taken up by the blood in compressed air. Carbon dioxide has therefore nothing whatever to do with the symptoms.

In order to obtain quantitative ideas as to the extent of the danger and the proper means of obviating it, the process must be considered more closely.‡ Symptoms of caisson disease are seldom, if ever, observed unless the excess of atmospheric pressure has exceeded one atmosphere or 15 pounds to the square inch. Hence a considerable excess of nitrogen must be present in the blood—in other words, it must be greatly supersaturated—in order that dangerous bubbling may occur. As the pressure is increased the risk of caisson disease increases, and becomes very formidable with an excess of two atmospheres, or 30 pounds, if the decompression is rapid.

* *La Pression Barométrique*, 1878.

† A very full account of the whole subject is given in Hill's recent book *Caisson Sickness*, 1912.

‡ See Boycott, Damant, and Haldane, *Journ. of Hyg.*, p. 342, 1908, where references to other literature will also be found; also Japp, *Proc. Amer. Soc. of Civil Eng.*, xxxv. 378, 778, 1909; and Keays, "Compressed-Air Illness." *Publications of Cornell University Medical College*, October, 1909.

On the other hand, the risk depends on the extent to which the venous blood has had time to become fully saturated at the increased pressure. It is evident from the foregoing discussion of gaseous exchange between the alveolar air and the blood, and from the fact that nitrogen is relatively insoluble in blood and enters into no chemical combination, that the blood passing through the lungs will practically saturate (or desaturate) itself completely with nitrogen at a single passage through the lungs. But when a man first enters compressed air his arterial blood will yield up nearly all its extra charge of nitrogen to the tissues surrounding the systemic capillaries. It will evidently be a long time before the tissues are fully charged up with nitrogen, so that the returning venous blood is also fully saturated. This time will also vary in different parts of the body, according to the activity of the local circulation and the capacity of the surrounding tissues for dissolving nitrogen. In this respect it is also very important that fatty substances have, as was shown by Vernon, a far greater capacity for dissolving nitrogen than blood or water possesses. Fat animals have been shown by Boycott and Damant to be much more susceptible to caisson disease.* The risk of bubble formation in the capillaries and veins will thus depend on the time of exposure to compressed air, and will vary in different parts of the body; and the time during which this risk continues after decompression will vary in a corresponding manner, since some parts will desaturate themselves much more slowly than others. The rate of saturation and desaturation can only be determined by experiment, and will evidently vary in different animals. Small warm-blooded animals, with very rapid respiration and circulation, will saturate and desaturate quickly; and, as a matter of fact, they are far less liable to caisson disease than large animals such as man, since the time during which risk continues after decompression is much shorter in their case.

From experience in compressed air work, and from experiment on goats, the results being corrected for the more rapid circulation in these animals, it appears that about three to five hours are needed for the human body to become practically saturated with nitrogen in compressed air. Up to this period the danger of decompression increases, but not beyond it.

The danger will evidently also increase with the rate of decompression. If the decompression is sufficiently slow, the excess of nitrogen will escape by the lungs quickly enough to obviate any dangerous state of supersaturation in the blood and tissues; and slow decompression is evidently the correct method of preventing caisson disease. Calculation will show, however, that if parts of the body take several hours to become fully saturated, these same parts will take many hours to desaturate at such a rate as will

* *Journ. of Hyg.*, p. 445, 1908.

obviate risk; for unless the process is extremely slow they will be supersaturated, at the end of the decompression, to an extent exceeding one atmosphere of pressure, so that there will be risk of bubbling. Experiment has shown, however, that just as the absolute barometric pressure may be safely reduced from two atmospheres to one, so it may be safely reduced from four atmospheres to two, or six to three. The danger depends, in other words, on the relative, and not on the absolute, reduction of pressure. There is just the same risk of caisson disease in reducing the pressure rapidly from one atmosphere to a third of an atmosphere as in reducing it from three atmospheres to one.

The method of stage decompression, recently introduced by Boycott, Damant, and the writer, and adopted in the Royal Navy for diving work,* takes advantage of this principle in order to shorten the period needed for safe decompression. The pressure is first reduced to half the absolute barometric pressure. This reduction leads to a very rapid unloading of the excess of nitrogen from the body, so that it is soon safe to reduce the pressure further; and in this way the diver or caisson worker is brought out safely in stages, the time required being much shorter than when uniform decompression is employed. To increase the rate of circulation, and thus hasten the elimination of the nitrogen, muscular exertions are continued during each stoppage, and the air-supply is diminished, so as to increase the percentage of $CO_2$ in the air of the helmet. In the case of divers, the saving of time and decrease of risk are particularly striking. It should be noted, however, that mere discontinuous decompression, without proper regard to the timing and spacing of the stoppages, may be wholly useless. Some misunderstanding has arisen through failure to realize this point. Recent observations made by Bornstein, in connection with the Elbe tunnel, indicate that the association of muscular work with decompression greatly diminishes the risk of at any rate the minor symptoms of caisson disease.

If symptoms of caisson disease have appeared, by far the most effective treatment is to recompress the patient, and this is now often done in a special medical recompression chamber. The bubbles are at once greatly reduced in size, and the symptoms often disappear promptly, but are apt to reappear unless the utmost caution is used in subsequent decompression. Time must be given for the bubbles to redissolve. This they must gradually do, for the total partial pressure of the nitrogen dissolved in the blood or tissues is always less than that in the bubbles, and may be much less at first. In the venous blood or in the tissues the total gas pressure cannot (except on decompression) exceed about 90 per cent. of the external atmosphere, whereas in a bubble it would be 100 per cent. Whether

* Report of the Admiralty Committee on Deep Diving, *Parliamentary Paper*, C.N. 1549, 1907.

or not recompression has been adopted, the bubbles (if they do not prove fatal) must ultimately disappear, just as any other collection of air within the body disappears. But if they have been allowed to block the circulation for long enough, they may have caused irreparable damage from local deprivation of oxygen. Secondary hæmorrhage may also have occurred and caused further damage, and permanent paralysis or other injury may result. It will also be readily understood that pre-existing debilitating causes must greatly increase the risk of such damage, since the recuperative powers of the vessels and tissues are diminished. Previous medical examination is thus very necessary in the case of men working in compressed air, and fat men should be excluded.

## CHAPTER XII

# THE PHYSIOLOGY AND PATHOLOGY OF TEMPERATURE

By M. S. PEMBREY

**Introduction.**—Disorders in the temperature of the body have attracted from the earliest times the attention of both the layman and the physician. An abnormal heat of the body, such as characterizes many diseases, can be felt both by the patient and his attendants. No special means are required for the discovery of such a disorder; it is apparent to the sense of temperature that the feverish patient is hotter than the healthy man. Most of the ancient writers* upon medicine considered heat as the chief sign of acute disease, and constantly directed attention to the temperature of the body. They made numerous observations, but were unable to extend their knowledge beyond the limits imposed by their sensations of heat and cold. The senses are a guide, but they are unreliable, for the sensation of temperature arises in the cutaneous nerves, and is affected by local changes which may be no indication of the condition of the whole body. The patient especially may draw wrong conclusions concerning the heat of his body. Thus, during the shivering stage of a fever he feels cold, although the internal temperature of his body is abnormally high; his skin is cold, and it is there that his sensations arise. The opposite mistake he makes during the sweating stage of the fever; he feels uncomfortably hot, for his skin is flushed and hot at a time when his internal heat may be below the normal. In a similar manner the physician is liable, owing to differences in his own cutaneous temperature and that of the patient, to form wrong estimates of the temperature of his patient.

Exact knowledge only became possible after the introduction of the thermometer† towards the close of the sixteenth century.

* See the historical account given by Lorain, *De la Température du Corps Humain*, Paris, 1877, t. i.; or Wunderlich, "Medical Thermometry," *New Syd. Soc.*, translation, 1871.

† Holloway, "The Evolution of the Thermometer," *Science Progress*, London, 1895-96, vol. iv., p. 413; Liebermeister, *Handbuch d. Path. u. Therap. des Fiebers*, Leipzig, 1875, s. 3.

The credit of the invention appears to be due chiefly to Sanctorius, the professor of medicine in Padua, and to his contemporary Galileo. Improvements in the construction of the thermometer were made gradually, but its use in medicine was for years almost unknown. One of the first to recognize the value of the thermometer in clinical work was Boerhaave, the celebrated professor of chemistry, botany, and medicine, who attracted numerous pupils to Leyden during the early years of the eighteenth century. In England some of the earliest and most valuable work on temperature was done by Martin, John Hunter, Crawford, James Currie, Benjamin Brodie, and John Davy; but many years elapsed before the thermometer was in general use in the hospitals and medical schools.

The use of the thermometer is now universal, but familiarity has led, unfortunately, in many hospitals, to an unwarranted neglect of the precautions which are necessary for exact investigation. The results, moreover, are not comparable; in some institutions the custom is to observe the temperature in the mouth, in others in the axilla, and in others in the rectum. Clinical records are published, often without any reference to the part of the body in which the temperature was observed, or to the time of day at which it was taken. A great advance would be made if the deep and surface temperatures of the body during different diseases received more attention from the physician. The thermometer is an instrument of precision, which should be used intelligently, and should not be abandoned to the nurse. Evidence will be given later to show that the distribution of heat in the different parts of the body is more important than the internal temperature.

It is impossible to consider adequately disorders of temperature unless there be a previous examination of the temperature of healthy men, its regulation, and the variations which it undergoes in response to internal and external changes. No attempt will be made to give a full account of the physiology of the subject,* but attention will be drawn to the parts which are of special interest in relation to pathology, and references will be given to enable the reader to consult the literature of the subject.

## The Temperature of Man in Health.

The knowledge of the internal heat of the human body is very incomplete, notwithstanding the numerous observations which have been made. This is in part due to the fact, already mentioned, that physicians have failed often to recognize that observations made in different parts of the body are not comparable. The

* For general accounts and literature, see the following: "Animal Heat," by Pembrey, in *Textbook of Physiology*, edited by Schäfer, 1898, vol. i., p. 785; "Chaleur," by Richet, in *Dictionnaire de Physiologie*, 1898, t. iii., p. 81; "Die Warmeökonomie des Körpers," by Tigerstedt in *Handbuch der Physiologie des Menschen*, by Nagel, 1906, Bd. i., 2ter Hälfte, s. 557.

mouth is liable to local variations in temperature, due to the cooling of its walls externally by evaporation of sweat and by contact with cold air, and internally by breathing. A thermometer, even if it be retained for ten minutes under the tongue in the closed mouth, may not indicate the true internal temperature of the body. The buccal temperature may be equal, or almost equal, to that of the rectum, if the subject be kept in warm surroundings or lying in bed shielded from cold; but, under ordinary conditions, a considerable difference will be found in a series of comparative observations. The rectal temperature is about 0·7° (1·26° F.) higher than that of the mouth and axilla. The temperature observed in the stream of urine as it issues from the urethra is about 0·3° (0·54° F.) lower than the rectal temperature. The axilla should be closed tightly, and long enough for the skin of the fold of the axilla to acquire the temperature of an internal cavity. In practice, this condition may not be obtained owing to the thinness of the subject. The same precautions must be taken in the case of the groin.

If exact results are required, the internal temperature should be observed in the rectum, mouth, and axilla; this applies both to healthy men and to patients suffering from disease. During muscular work the temperature of the rectum rises, it may be a degree or two Fahrenheit, and at the same time the temperature of the mouth may show a fall. In patients suffering from cardiac dyspnœa, or a rigor, there may be considerable differences between the buccal and rectal temperatures. A knowledge of the distribution of heat is of much greater value than a single record of the temperature.

**The Normal Internal Temperature of Man.**—There is no doubt that different individuals maintain their temperature at slightly different levels, even when they are apparently in good health, and are living under conditions as far as possible the same. There is in the regulation of temperature, as in all physiological processes, a certain range of health; there is no fixed standard. The mean daily temperature is about 37° (98·6°), the maximum about 37·5° (99·5°), and the minimum about 36° (96·8°); these are to be considered as average figures for men who are not engaged at the time of the observations in muscular work.

It is necessary to draw further attention to the incompleteness of the data upon the temperature of healthy men. The mean daily temperature refers in most cases to the average temperature during an ordinary day, not during a day and night of twenty-four hours. There are but few observations taken during the night-time, when the lowest temperatures are observed; for this reason the figure given for the minimum does not represent in most of the cases the true minimum. The maximum of the daily curve occurs during the working day, and is therefore more truly represented in the

figure given; it is, however, not the maximum which is observed after exercise.

**The Daily Variation of Temperature and its Causes.**—The temperature of a healthy man shows a daily variation—it rises during the day, the time of activity and work; it falls during the night, the time of rest and sleep. This relationship to night and day would suggest that the cause of the variation is to be sought chiefly in muscular activity. The differences in the times of the maximum and minimum found by various observers are to be explained by variations in the routine of life of the subjects of the observations. The nature of the daily variation is shown by the curves on pp. 502 and 503 (Figs. 17 and 18).

Reversal of the routine of ordinary life, such as that found in night-workmen, tends to a reversal of the curve of temperature; this is not seen to the full extent in the first night of work, for it is well known that towards the time of the natural minimum of temperature, about four o'clock in the morning, the night-watcher experiences a great inclination to sleep, but as the hours pass by he finds that this desire becomes less and less imperative. The capacity of the human body to adapt itself to different conditions of life is exceedingly great, but time is required for accommodation. This, in respect of temperature, is shown by the results obtained by Benedict and Snell.*

The best proof of the dependence of the daily variation in temperature upon activity and rest is supplied by Sutherland Simpson and Galbraith,† who have observed the temperature of nocturnal birds; the curve rises during the night and falls during the day.

The daily variation in temperature is not due to food, for the observations of Jüngensen,‡ and of Benedict and Snell, upon fasting men show that the curve is similar to the ordinary type.

The temperature of a healthy man lying in bed during twenty-four hours shows a daily variation which resembles his ordinary curve, although the maximum is not so high. This fact has been brought forward as an argument against the view that muscular activity is the cause of the variation in temperature. It cannot, however, be accepted as such. Even during rest in bed there is more muscular activity than during sleep, and the observations of Tigerstedt have shown that restlessness, or even very slight muscular movement, is accompanied by increased combustion; this can be prevented only by constant attention to the maintenance of muscular inactivity. The influence of daylight is to be attributed, in very great measure, to the natural association of increased activity. The daily curve of temperature is not marked in infants, for during

* *Amer. Journ. Physiol.*, 1904, vol. xi., p. 145.

† *Journ. Physiol.*, 1905-6, vol. xxxiii., p. 225.

‡ *Die Körperwarme des Gesunden Menschen*, Leipzig, 1873.

the first few weeks after birth there is no definite sequence of activity and rest; this the mother will soon enforce, or at least attempt to enforce, upon her child.

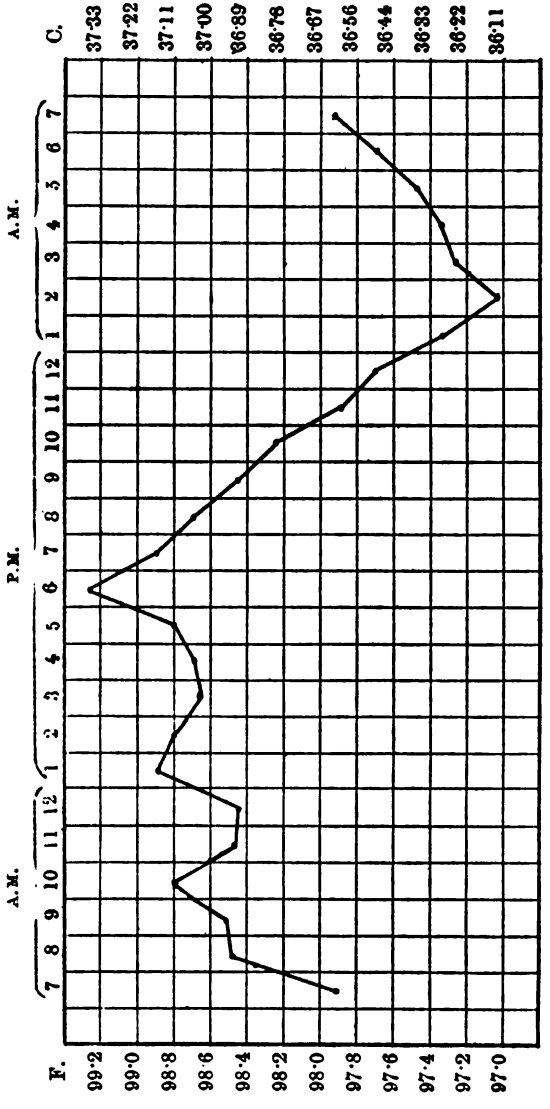



FIG. 17.—DAILY VARIATION IN RECTAL TEMPERATURE OF MAN.*

* Pembrey and Nicol, *Journ. Physiol.*, 1898-9, vol. xxiii., p. 386.

**The Influence of Sleep** upon the temperature is similar to that of muscular inactivity; it causes a fall in temperature, and is accompanied by a diminished control over the regulation. The muscular

tone is reduced, and the reflex responses to external temperature are evoked less readily. Sweating is sometimes observed in sleeping children and adults when there is no obvious disorder of health or

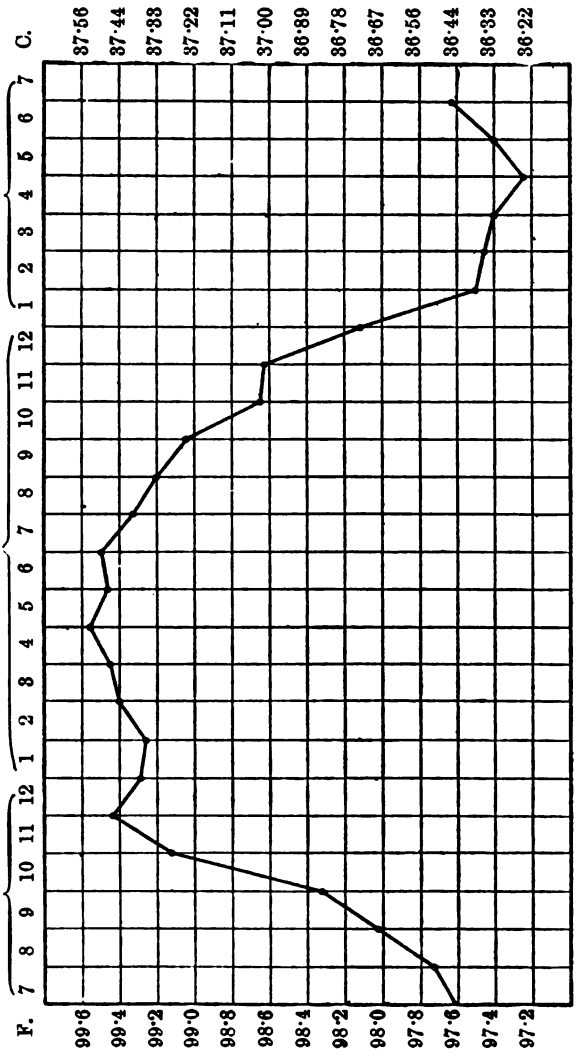



FIG. 18.—DAILY VARIATION IN TEMPERATURE OF MAN.*
The observations were made by placing the bulb of a clinical thermometer in the stream of urine as it issued from the urethra.

* Pembrey and Nicol, *Journ. Physiol.*, 1898-9, vol. xxiii., p. 886.

external heat; it would appear to be due to the decreased efficiency of the regulation of temperature. The night-sweats which are characteristic of certain cases of disease will be considered later.

**The Influence of Mental Work** upon the temperature has been the subject of considerable discussion, for the results of different

observers are discordant. Mental activity is accompanied in most cases by a decrease in muscular tone, but in others the opposite is seen; herein may lie the cause of the disagreement just mentioned.

**The Influence of Muscular Work.**—Exercise is accompanied by a greatly increased respiratory exchange and production of heat, which, in the absence of a greater loss of heat, will raise steadily the temperature of the body. In fact, under conditions of health, a certain rise does occur even during moderate work; the rectal temperature is raised a degree or two Fahrenheit, but shows no further rise during a continuation of the work. Compensation is effected by increased loss of heat, due to the flushing of the cutaneous vessels, sweating, and more rapid or deeper breathing. A rise of rectal temperature to 38·33° (101°) is not accompanied by any pathological effect or even by discomfort. During muscular work, such a rise must be considered physiological and favourable to the performance of work. It has been shown recently by Barcroft and A. V. Hill* that oxyhæmoglobin gives off oxygen more readily at a high temperature; the supply of oxygen will be facilitated by the rise of temperature produced by muscular exercise.

This increased heat of the body has been overlooked or even denied by many observers; for this reason, and on account of its practical importance, it is necessary to seek some explanation for the disagreement in results. There is little doubt that this is to be found in the fact that the determinations of the temperature of the mouth before and after work are unreliable; the temperature of the mouth often falls, while that of the rectum is rising.† This is especially the case in cold weather, for the walls of the mouth are cooled externally by the evaporation of sweat and by contact with cold air, and internally by breathing. When the work or exercise is finished, the rectal temperature returns rapidly to the normal, or even becomes subnormal.

In animals, both domesticated and wild, a rise of temperature during exercise has been found apparently in every investigation; the temperature has been determined almost invariably in the rectum.

The practical importance of this subject will be indicated later in relation to the influence of external heat, moisture, and clothing, and the pathology of so-called "heat-stroke." Here it may be pointed out that a rise in temperature during muscular exercise is no reason for ordering a consumptive patient‡ to his bed; by progressive exercise his general condition and resistance to his disease can be greatly improved.

**The Influence of Food** upon the temperature of the body is complicated by muscular activity, both local and general. During, and often

* *Journ. Physiol.*, 1909-10, vol. xxxix., p. 411.

† For a critical account and experiments, see paper by Pembrey, Arkle, Bolus, and Lecky, in *Guy's Hospital Reports*, 1902, vol. lvii., p. 283.

‡ Bardswell and Chapman, *Brit. Med. Journ.*, 1911, vol. i., p. 1106.

for a short time after, a meal there is a condition of comparative rest, which in itself would result in a fall of temperature. The muscles of mastication and the salivary glands are active during the meal, and their activity is accompanied by a production of heat, and by a more abundant and rapid flow of blood through those parts. These conditions will raise the temperature of the mouth. Other local factors come into play. Food and drink may be taken either hot or cold; by drinking tea or coffee at the usual temperature of 50° to 60° (122° to 140°), the temperature of the mouth may be raised for a short time above that of the rectum.

The temperature of the body may be raised two or three tenths of a degree by a meal, but the daily variation in bodily heat is very similar, whether a man is well fed or fasting. More heat is produced in the first case; but, owing to the efficiency of the regulation, the temperature is maintained at a similar height in both cases. Observations upon fasting men do not show any definite fall in temperature or any appreciable decrease in the production of heat during the condition of rest; but it is necessary to remember that they cannot resist easily the action of cold. Their exchange of material and production of heat are reduced, and they can meet the demands of the body for heat only by the combustion of their reserve material, after the loss of heat has been reduced as much as possible by the constriction of the cutaneous bloodvessels.

**The Influence of External Temperature, Moisture, and Wind.**— The temperature of a healthy man is fairly constant, and does not differ more than a degree or two Fahrenheit, whether he be living in the Arctic Regions or in the Tropics; he is able, more readily than the higher animals, to adapt himself to extremes of heat and cold. This capacity is to be ascribed in part to a greater perfection of the power of regulation, the naked condition of the skin, and the great development of the vasomotor system and sweat-glands; but also to the power which man possesses of mitigating the effects of extremes of temperature by the selection of suitable clothes, food, and shelter. Even with all these advantages, the capacity of the most civilized people to resist changes of temperature is limited, and is even curtailed by some of the characteristic developments of civilized life. The limitation of natural ventilation by the dense aggregation of lofty houses, the exigencies of work, and the dictates of fashion in clothes and the routine of life, have imposed an extra strain upon the natural capacity of man. This is seen in the suffering which the dwellers in large cities in Europe and America undergo whenever a heat-wave passes over their countries. Time is required even for natural accommodation, and much more for the adaptation of the mode of living and dress, which are determined so largely by convention or fashion.

Muscular work in hot climates or surroundings must be limited, otherwise too great a stress will be thrown upon the power of

regulation. This danger is seen especially among miners working in hot mines, stokers feeding furnaces, and soldiers marching in close order, badly laden and unsuitably clothed during hot weather. In all of these cases it is well known that the important factor is not the absolute temperature, but a combination of a high temperature with a moist and stagnant atmosphere. Blagden and Fordyce* showed, by observations upon themselves in 1775, that the effect varies according to the amount of moisture present in the air. They remained for fifteen minutes in a damp room heated to 54·4° (129·9°), and found that the temperature of their mouths and urine rose to 37·8° (100·04°); but, after a similar exposure in a dry room heated to 115·5°–126·7° (239·9°–260·06°), they observed no rise in their temperature, although the room was so hot that beef-steaks were cooked by the heat of the air.

It is unnecessary to refer to the numerous experiments which have been made upon this subject, both in the case of men and animals;† but some account must be given of the observations of Haldane,‡ for they not only indicate the limits of heat and humidity which can be borne safely for considerable periods, but also have an important bearing upon the pathological effects produced by a hot, moist atmosphere. Haldane's first experiments were made in Dolcoath Mine in Cornwall, where, owing to various difficulties, the ventilation was inadequate, and the temperature was maintained at a high point by the oxidation of iron pyrites. He remained for two hours and eighteen minutes in a "level" where the ventilation was suspended, and the temperature of the air was 34·44° and 34·22° (94° and 93·6°) by the dry and wet bulbs respectively. During this time his rectal temperature rose to 40·11° (104·2°), the rate of his pulse was 164 per minute, and he suffered from much throbbing in the head and general discomfort; no work was performed during the experiment, and the only clothes worn were flannel drawers, canvas trousers, boots, and stockings. From numerous other experiments upon himself and other subjects, Haldane draws the following general conclusions: "The rectal temperature did not show any abnormal increase during rest in still air until the temperature by the wet-bulb thermometer reached about 31° (88°), provided the subjects were stripped to the waist or clad in light flannel. If, however, the wet-bulb temperature exceeded this temperature by even one degree, a very marked rise in rectal temperature occurred. This was observed in each of the subjects investigated, and took place whether the air temperature was the same as the wet-bulb temperature or 28° (50°) above it, or only about 5·56° (10°) above it. In proportion as the wet-bulb temperature rose beyond 31·11° (88°) by wet bulb, the rise of rectal

* *Phil. Trans.*, London, 1775, vol. lxv., pt. i., pp. 111, 484.
† See "Animal Heat," *loc. cit.*
‡ *Journ. Hyg.*, 1905, vol. v., p. 494.

temperature became more and more rapid. Thus, at 31·67° to 32·22° (89° to 90°) wet bulb, the rise was about 0·56° to 0·78° (1·0° to 1·4°) per hour; at about 34·4° (94°), the rise was about 1·1° (2°) per hour; and at 36·4° (98°), the rise was about 2·2° (4°) per hour. In moving air a higher wet-bulb temperature could be borne without abnormal rise of rectal temperature. Thus, in an air-current of about 170 linear feet (50 metres) per minute, a wet-bulb temperature up to about 34·4° (93°) could be borne without abnormal rise of bodily temperature.

"During muscular work in still air, the limit of wet-bulb temperature which could be borne without abnormal rise of body temperature was much lower. Thus, during leisurely climbing work (13 feet per minute), the limit for a person stripped to the waist was about 25·5° (78°) or 5·56° (10°) lower than during rest, and with harder work this limit would certainly be lower. At a wet-bulb temperature of about 30·5° (87°), the rectal temperature rose about 1·94° (3·5°) in an hour. In an air-current of about 135 linear feet (41 metres) per minute, a wet-bulb of about 29·5° (85°) could be borne without abnormal rise of body temperature, but 30·5° (87°) was beyond the limit.

"The symptoms observed to accompany the rise of body temperature were—(1) A marked increase in the pulse-rate, accompanied by throbbing in the head; (2) dyspnœa, particularly on any exertion; and (3) a general feeling of exhaustion and discomfort.

"The increase in the pulse-rate was usually about 20 beats per minute for each 1° F. of increase in rectal temperature, or 36 beats for each 1° C., while the subject was standing in the warm air, the increase being about a fourth less in the sitting posture. On returning to cool air, there was, however, an immediate drop in the pulse-rate, so that the increase in the pulse-rate was only about 10 beats per minute per 1° F. of increased rectal temperature in the standing position, and 8 beats sitting. The increase in pulse-rate thus depended not merely on the rectal temperature, but also on the external (wet-bulb) temperature.

"The hyperpnœa was not noticeable until the rectal temperature exceeded 38·89° (102°). At 39·44° (103°) it was marked during muscular work, and distinctly noticeable during rest."

The influence of high temperatures on the human body, especially with regard to the causation of heat-stroke, has been investigated by Sutton,* who finds that there is a distinct tendency to parallelism in the rise of the temperature of the body and the increase in the respiratory exchange. The application of these conclusions to questions of general pathology will be considered later, when the subjects of heat-stroke and fever are discussed.

A warm, stagnant, and moisture-laden atmosphere has a depressing effect upon the people exposed to it. The effect of work

* *Journ. Path. and Bact.*, 1909, vol. xiii., p. 62.

under such conditions is to increase the temperature, pulse, and loss of moisture, out of proportion to the work done. Efficient work cannot be performed unless the temperature of the body is prevented from rising above a certain optimum. The temperature depends upon the production and the loss of heat; work increases the production, and the passage of more blood through the vessels of the skin and the evaporation of sweat increase the loss. A warm, moist, and stagnant atmosphere hinders the loss and taxes the power of accommodation of the worker. The result is that he either does less work, or unwisely neglects the warning which he receives from his sensations, and works at an uneconomical rate to the detriment of his health.

When the temperature of the air is high, both by the dry and wet bulb thermometers, the evaporation of sweat must be greatly increased in order to cool the body. This is shown by a comparison of the following results, obtained upon soldiers when they performed a march of seven miles on hot and cold days with the same clothing, equipment, and load:

| | Four Men on Hot Day. | Four Men on Cold Day. |
|---|---|---|
| Increase in pulse per minute: | | |
| Maximum .. .. .. .. | 84 | 24 |
| Minimum .. .. .. .. | 52 | 8 |
| Average .. .. .. .. | 62 | 14 |
| Increase in rectal temperature (Fahrenheit): | | |
| Maximum .. .. .. .. | 2·3° | 1·6° |
| Minimum .. .. .. .. | 0·6° | 0·0° |
| Average .. .. .. .. | 1·4° | 0·8° |
| Loss of moisture from body in grammes: | | |
| Maximum .. .. .. .. | 2,390 | 555 |
| Minimum .. .. .. .. | 1,140 | 300 |
| Average .. .. .. .. | 1,816 | 419 |
| Increase in weight of clothes in grammes: | | |
| Maximum .. .. .. .. | 640 | 40 |
| Minimum .. .. .. .. | 60 | 0 |
| Average .. .. .. .. | 320 | 27 |
| External temperature (Fahrenheit): | | |
| Dry-bulb .. .. .. .. | 79° | 45° |
| Wet-bulb .. .. .. .. | 67·5° | 38° |

Hot, moist climates have a depressing effect. There is a certain range of temperature which is most suitable for man; extremes of heat and cold are opposed to his greatest development. There is, indeed, much to be said in favour of the much-abused climate of England; in few countries is it possible to enjoy so much open-air work or exercise all the year round as in this country, and the

variability and uncertainty of the climate has been, and doubtless is still, an important factor in the development and maintenance of the national characteristics. Variations in external temperature stimulate the nervous system to develop its control of the various functions of the body and its power of adaptation.

Even in this country many workers, such as miners* and weavers†, are exposed to hot, moist air. The general effect‡ is to diminish the difference between the internal temperature and that of the peripheral parts of the body, to establish a more uniform temperature of the body as a whole, and to throw a tax upon the powers of accommodation.

A wet-bulb temperature of 23·9° (75°) has been taken as the legal limit for the temperature of cotton-weaving sheds in this country. This temperature in the outside air is rarely reached in England, but during heat-waves in the United States of America a wet-bulb temperature of 25·5° (78°) has been associated with great distress and many deaths among the inhabitants of large cities.

The influence of cold is seen in greater muscular activity and general alertness; the difference between the temperature of the peripheral and internal parts is greater than in warm surroundings, and this produces a greater tone of the muscular and vascular systems. Cold has a stimulating effect; increased muscular activity is accompanied by increased combustion, and this in turn augments the appetite. Such conditions are favourable to sturdy and active growth; for this reason English children are sent home to escape the depressing effects of the Indian climate. Other examples of medical importance are the tonic effect of cold baths and the open-air treatment of consumption. A cold bath in the morning is of value, not so much for its cleansing properties as for the stimulating effect which it produces upon the nerves and muscles of the body. The skin is subjected to a sudden change from the warmth of the bed, and thus the nervous system of the man is trained to meet variations of temperature; his cutaneous vessels contract, and thus prevent undue loss of heat. By practice he becomes immune to the effects of changes of temperature and less liable to chills. In the case of the open-air treatment of phthisical patients, there is little doubt that it is the free exposure to variations of temperature, moisture, and wind, which produces the beneficial effect.

**The Influence of Age.**—The capacity to maintain a constant temperature has been evolved in the animal series and in the individual warm-blooded animal. An infant at birth does not possess the

* Haldane, Martin, and Thomas, Report on the Health of Cornish Miners, *Parliamentary Papers*, 1904, p. 93.

† "Humidity and Ventilation in Cotton-Weaving Sheds," *Parliamentary Papers*, 1909 and 1911.

‡ Collis and Pembrey, Proc. Physiol. Soc., *Journ. Physiol.*, 1911, vol. xliii

power of maintaining a constant bodily temperature, and its temperature will fall if it be taken away from the heat of its mother's body and exposed to moderate cold. A weak or premature infant shows this inability in a more marked degree. The practice of the modern nurse is to take the newly-born infant away from its mother, in order that the infant may breathe purer air and the mother may not be worried; this is opposed to instinct and physiological knowledge. The infant requires warmth; to slight alterations in the gaseous composition of the air it is less sensitive than the adult. The risk of overlaying arises almost entirely from drunken mothers, and is much less serious for the race than the undermining of maternal instinct and the treatment of maternity as a pathological condition or illness; the cherishing of the young infant is to the natural mother neither a hardship nor a worry, but a comfort and the normal stimulus for rapid restoration after labour. If the babe cried, she would put it to the breast, and its suckling would favour the inflow of milk and the contraction of the uterus.

The variation in the temperature of infants during the first few days after birth has been investigated by Raudnitz.* Sponging with cold water produces a rise in the rectal temperature of strong infants, but in weaklings the temperature remains stationary or falls. These results have been confirmed and extended by Babák.† The temperature of infants is low, even when they are fully clothed and are kept in a room at 15° (59°); in infants an hour or two old, the temperature may be as low as 34° or 35° (93·2° or 95·0°). It rises gradually during the first day or two, but is liable to considerable variations; thus, on the fifth day after birth, the rectal temperature varied from 36·2° to 33·5° (97·16° to 92·3°) in an infant weighing 2,550 grammes (5·6 pounds), and kept in a room at 12° (53·6°). The regulation of the loss of heat is imperfect, and this is shown if an infant be clothed insufficiently when it is exposed to even moderate cold; its temperature falls. The regulation of the production of heat by variations in combustion is also incomplete, and only within narrow limits can the newly-born infant respond to changes of temperature in a similar manner to the response of the adult.

For the reasons just given, a rise or fall in the temperature of infants is of less clinical significance than a corresponding change in the temperature of an adult. A fit of screaming which is accompanied by considerable muscular activity will raise the temperature of a healthy infant to a height which might be considered pathological. Too cold a bath, or exposure to cold after a warm bath, may lower the temperature of an infant 4° or 5° C. (7° to 9° F.).

* *Zeitschr. f. Biol. München*, 1888, Bd. xxiv., s. 423.

† *Arch. f. d. ges. Physiol.*, Bd. lxxxiv., s. 171.

The following curves (p. 512), obtained by Jundell,* show that the daily variation in temperature is not indicated in infants about a week old, but is gradually established. This is due, no doubt, to the gradual development of a periodicity—rest during the night and activity during the day. In a young infant the range of temperature is for a similar reason less than that seen in a young child or an adult, unless exceptional conditions, such as external cold, are present.

In aged subjects the exchange of material in the body is much less active than in the adult, and the capacity to accommodate for changes in external temperature becomes less and less; for not only are muscular activity and production of heat diminished, but enfeeblement of the circulation impairs the power of regulating the loss of heat. Old people often suffer much from the effects of extremes of weather.

**The Influence of Race.**—There appears to be no difference in the temperature of various races; any variations are to be attributed to the effect of the climate, clothing, and work. The European can adapt himself to the temperature of any inhabited country. His resistance to the conditions of life may be less than that of the natives; but here other factors come into play, such as the absence of the pigment, which protects the inhabitants of tropical countries from the influence of the chemical rays of the sun, the routine and mode of life, food, and immunity to disease. The experience of Englishmen shows that time is required for adaptation to the life in India, and even to that in England when they return after an absence of several years. The European is able to withstand the heat of a stokehold even better than the coloured man, for in this case the pigment of the skin gives no advantage; he is able also to resist the extreme cold of the Arctic regions as well as the Esquimaux. This power of endurance is to be attributed in a great measure to his superior mental development and strength of will. Nevertheless, there is little doubt that the best growth of the characteristics of the white races obtains in temperate climates.† English women and children do not adapt themselves readily to a hot, moist climate, such as that of some parts of India.

**The Influence of Sex.**—When allowance is made for differences in the routine of life of men and women, there is no definite influence of sex upon the temperature of the body.

**The Influence of Menstruation, Pregnancy, and Parturition.**—In healthy women these physiological conditions have no special effect upon the temperature.

**The Influence of Clothing.**—Under ordinary conditions, only the face and hands of Europeans are exposed freely to the air; the body

* *Jahrb. f. Kinderheilk.*, N. F., 1904, Bd. 69, s. 521.

† See p. 518.

FIG. 19.

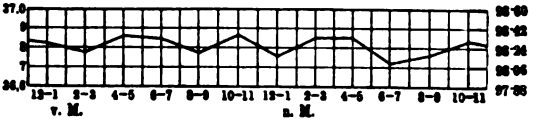



FIG. 20.

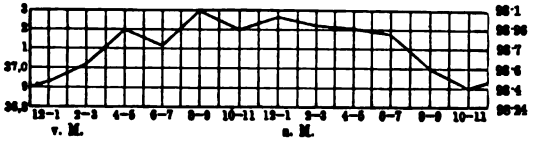



FIG. 21.

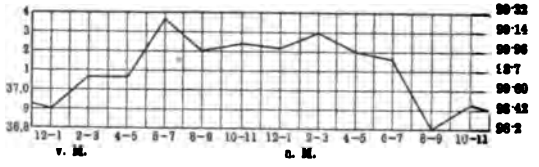



FIG. 22.

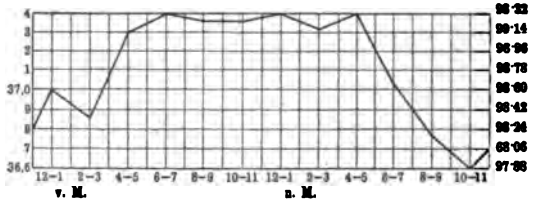
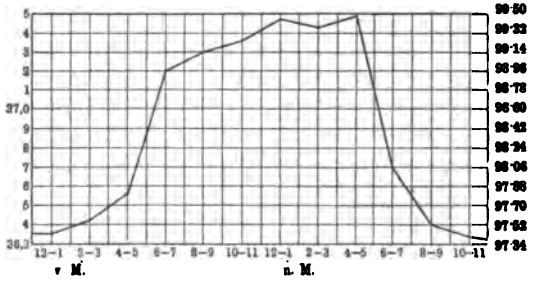



FIG. 23.




FIGS. 19 TO 23.—DAILY VARIATION IN THE TEMPERATURE OF INFANTS AT DIFFERENT AGES (JUNDELL).

Fig. 19, Five to eight days; Fig. 20, one month; Fig. 21, end of second to beginning of third month; Fig. 22, six months; Fig. 23, from second to fifth year. v. M. = a.m.; n. M. = p.m.

and limbs are protected by clothes, and are surrounded by a layer of air, with a temperature intermediate between the temperature of the skin and that of the external air. The main purpose of clothing is found in this inclusion of air; the different articles of dress form strata with different temperatures. In this way the greater part of the surface of the skin is exposed to air which is warm even when the external air is cold. The air included in the pores of the clothing and between the different articles of dress has been estimated at 20 to 30 litres. The radiation and conduction of heat from the skin are diminished by clothing, and thus the temperature of the skin is maintained at a higher point than it would be if the skin were uncovered; this higher temperature will increase the loss of moisture from the body, but the net result is still a saving of about 20 per cent. of the heat loss at a temperature of 15·55° (60°).

During muscular work in hot weather the clothes may retain large quantities of moisture, if there be no free circulation of air. The cooling effect of sweating is partly lost in such cases, for it takes place from the surface of the clothes, and only affects the skin through the layer of damp underclothing. The opening of the jacket, waistcoat, and shirt, will bring about not only comfort, but also the most effective use of the moisture discharged from the body. There is no doubt that the greatest discomfort arises when the temperature of the skin is abnormally raised. It is in the skin that the sensations of heat and cold arise. An increase in both the deep and surface temperature shows that the body is warmed in all its parts, and discomfort is then experienced; if, on the other hand, the skin be kept cool by sweating or exposure, no discomfort and no bad effects are experienced by a healthy man whose internal temperature has been raised a degree or two by hard work.

A man works more slowly when he feels too hot, or if he wishes to continue to work hard he increases the loss of heat from his skin by the removal of his coat and waistcoat, and by turning up his sleeves. Thereby the evaporation of sweat is facilitated, as shown by comparative observations * made upon soldiers after a march of seven miles (see table, p. 514). In both cases the men performed the same march with the same equipment and load; but in the first they did not wear their jackets, in the second they did.

The texture of clothing is important in relation to the freedom of ventilation and evaporation of sweat. In addition, the colour of the skin and clothing must be considered, for there are heat rays and chemical rays in sunlight. The pigmentation of the skin on exposure to the sun is due to a chemical change of metabolic products, and not to altered hæmoglobin. The antecedents of

* "Committee on Physiological Effects of Food, Training, and Clothing in the Soldier," Second and Fourth Reports, 1908 (*Journ. Royal Army Medical Corps*, 1909, vol. xii., p. 211, and 1909, vol. xiii., p. 592).

the pigment, melanin, are probably decomposition products of protein, and circulate in the blood; the tissues possess specific ferments in their cells, and are able to convert the chromogens into pigments. Albinos can form hæmoglobin, but not melanins; they appear to lack the appropriate ferment, for they do not become sunburnt. Their skins become red from dilatation of the bloodvessels, but not pigmented.

| | Five Men in Drill Order without Jacket. | Five Men in Drill Order with Jacket. |
|---|---|---|
| Increase in pulse per minute: | | |
| Maximum | 52 | 48 |
| Minimum | 16 | 24 |
| Average | 28 | 41 |
| Increase in rectal temperature (Fahrenheit): | | |
| Maximum | 1·6° | 1·8° |
| Minimum | 0·6° | 0·8° |
| Average | 1·0° | 1·5° |
| Loss of moisture from body in grammes: | | |
| Maximum | 1,430 | 2,000 |
| Minimum | 1,000 | 1,200 |
| Average | 1,200 | 1,500 |
| Increase in weight of clothes in grammes: | | |
| Maximum | 250 | 480 |
| Minimum | 0 | 90 |
| Average | 109 | 254 |
| External temperature (Fahrenheit): | | |
| Dry bulb | 67° | 69° |
| Wet bulb | 58° | 59° |

The skin* of the white man becomes brown on exposure to the sun, and this pigmentation cannot be explained apart from a definite local action. A line of demarcation is seen round the neck, round the arms, and in children around the legs, and in each case it coincides with the limits of the clothing. It is not a question of increased temperature, but of exposure to the sunlight; the dilatation of the bloodvessels of the skin is not the cause, for this is seen in albinos, and they do not become sunburnt.

The pigmentation of the skin protects the body against the injurious action of certain rays of the sun. A negro can withstand exposure to intense sunlight which would be intolerable to a white man unprovided with clothing. This is not a question of exposure to heat, for it has been found that, as stokers on board ship or in furnaces, the coloured man is not superior, but even inferior, to the white man in resisting the effects of heat and moisture. The skin,

* For further details and references see "The Functions of the Skin," *Brit. Journ. Dermatology*, 1910.

unaccustomed to exposure, is readily irritated by the sun of an English summer; there is a great dilatation of the cutaneous bloodvessels, and this may be followed by inflammation and exudation of fluid, sufficient, in many cases, to form blisters. By gradual and continued exposure the skin becomes sunburnt, and is thus protected against the sun. Comparative experiments made by Eijkman* upon the skins of Europeans and of Malays living in the tropics have shown no difference in the radiation of heat, but a greater absorption of heat in the case of the brown skin of the Malays. There is little doubt that the pigment gives protection against the ultra-violet rays, but not against the heat rays. It absorbs the actinic rays, and this appears to be the reason why the photograph of a negro is indistinct when compared with that of a white man, whose skin reflects more light with actinic power. Pieces of frog's skin placed over sensitive photographic plates prove that the pigmented parts are very effective in absorbing the chemically active rays of light.

The question of clothing in the tropics has attracted considerable attention, and suggestions have been made that orange-red material should be used in order to exclude the actinic rays of the sun. Recently, extensive comparative tests† with orange-red and white clothings have been made by the United States Army in the Philippines. One group of 500 soldiers wore the special underclothing, and a similar number of controls were equipped with white underclothing. The conclusions drawn from the results of the experiments were that the effects of the climate in the Philippines can be, and probably are, produced by moist heat, and that, even if the actinic rays of the sun had any influence, they were sufficiently excluded by the khaki uniform and the campaign hat. The orange-red underclothing was heavier than the white, and increased the discomfort produced by heat.

Experience has guided mankind in the selection of clothing, and experience is the best guide. In some cases, however, convention, fashion, or military regulations, disregard the teachings of experience, and are responsible for great inefficiency, and even for the serious pathological condition of temperature seen in "heat-stroke."

**The Normal Surface Temperature of Man.**—The temperature of the skin is related to its vascularity and to its secretions. It is possible, therefore, to study it indirectly as well as directly. The colour of the skin is a guide to its vascularity—white when the vessels are uniformly contracted and contain but little blood; red when the vessels are dilated and well filled; and blue, or, as the saying is, "blue with cold," when the contraction is not uniform, and the blood is stagnant in some of the smaller vessels. The

* *Arch. f. path. Anat. und Physiol.*, 1895, Bd. cxl., s. 125.

† See abstract in *Journ. Royal Army Medical Corps*, 1911, vol. xvi., p. 109

extremes can be recognized easily, but it is impossible to fix a standard for health. Some healthy subjects have naturally a pale skin, although there is no lack of blood or blood-pigment in the body; it may be that their skin is not so vascular, or that the cutaneous vessels are in a state of greater tone. Other subjects have a very sensitive nervous control of their vessels; the skin of their extremities quickly responds to changes of external temperature. The reponse may be so pronounced that, on exposure to cold, their fingers and toes "die away," and become quite bloodless. This is not caused, as many suppose, by failure of the heart, but by a local cessation of the flow of blood due to a contraction of the small arteries, sufficient to withstand the pressure of the blood.

There are two methods in use for the determination of the temperature of the skin—the mercurial thermometer with a flat bulb, and the thermo-electric pile or needle. Good results can be obtained with the former method, as John Davy, Waller, and others, have shown. It is true that there may be sources of error, but these are more than counterbalanced by the ease with which observations can be made, as compared with the complicated apparatus required for thermo-electric work. This contention will be substantiated best by a comparison of the results obtained by different observers, some of whom have used the one method, some the other. The following table affords such a comparison:

| | Mercurial Thermometer. | | | | | | Thermo-Electric. | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | J. Davy.* | | M. S. Pembrey.† | | B. A. Nicol.† | | Kunkel.‡ | | G. N. Stewart.§ | |
| Temperature | ° C. | ° F. | ° C. | ° F. | ° C. | ° F. | ° C. | ° F. | ° C. | ° F. |
| of air .. | 21 | (69·8) | 10 | (50) | 19·5 | (67·1) | 20 | (68) | 18·3 | (64·94) |
| Forehead .. | — | | — | | — | | 34·1 | (93·38) | 33·04 | (91·47) |
| Hand (back) | — | | 26·25 | (79·25) | 31 | (87·8) | 32·5 | (90·5) | — | |
| ,, (palm) | — | | 30 | (86) | 32·5 | (90·5) | 34·4 | (93·92) | 30·95 | (87·71) |
| Forearm .. | — | | 30·8 | (87·44) | 33·4 | (92·12) | 33·7 | (92·66) | 34 | (93·2) ‖ |
| Arm .. .. | — | | — | | — | | — | | 35 | (95) ‖ |
| Chest .. .. | 34·44 | (93·99) | — | | — | | 34·6 | (94·28) | 34·57 | (94·22)‖ |
| Abdomen .. | 35 | (95) | 34 | (93·2) | 34 | (93·2) | 34·6 | (94·28) | 35·16 | (95·29) |
| Thigh .. | 34·44 | (93·99) | 33 | (91·4) | 32 | (89·6) | 34·2 | (93·56) | — | |
| Leg (calf) .. | 32·89 | (93) | 31 | (87·8) | 32 | (89·6) | 33·6 | (92·48) | — | |
| Foot (sole).. | 32·2 | (89·96) | — | | — | | — | | 31·05 | (87·89) |

An examination of the table shows that the temperature of the skin of the trunk is much more constant than that of the extremities.

* *Phil. Trans.*, London, 1814, vol. civ., p. 590; *Researches*, London, 1839, vol. i., p. 150.

† *Journ. Physiol.*, 1898-99, vol. xxiii., p. 386.

‡ *Zeitschr. f. Biol.*, 1889, Bd. xxv., s. 55.

§ *Stud. Physiol. Lab., Owens Coll., Manchester*, 1891, vol. i., p. 100.

‖ Temperature of air in this case =17·6° C. (63·68° F.).

There is no uniformity in the temperature of the healthy body; the temperature is not constant in health, notwithstanding the fact that it is often said to be so, and clinical thermometers and temperature-charts are marked with a line at 98·4° F. for the normal. The absence of uniformity is a sign of health and well-being. We are comfortable, and unconscious of the fact that there are local differences in temperature, which at once become manifest when we place our hands in succession on the face, chest, abdomen, and foot. As soon as the external conditions, such as heat, moisture, and absence of wind, become favourable for the development of a more uniform temperature of the body, discomfort and inefficiency arise. This question is one of the greatest importance in relation to the influence of climate and artificial systems of heating dwellings and workrooms, and it is unfortunate that many authorities have overlooked the physiological aspect. In living things there is no uniformity, and all attempts to obtain uniformity in religion, politics, work, or social standing, have failed. Uniformity would mean absolute stagnation—death.

The extravagant and dusty open fire is better than the closed stove, or the radiators filled with hot water or steam, for it produces more variations in the temperature of the room, and these act upon the skin. Changes in the temperature of the skin stimulate the nervous system, and produce a more steady growth and greater activity of the body and mind.

The value of determinations of the temperature of the skin lies not only in the data obtained for the distribution of heat in the body, but also in the evidence which, in conjunction with the values obtained for the internal temperature, it affords of the production of heat. If the internal temperature remains normal, and the surface temperature is increased, a greater production of heat is indicated, provided that the external conditions be the same. This line of argument can be extended to variations of both internal and surface temperature, and conclusions can be drawn upon the questions of the production and loss of heat in health and disease.

The conditions which influence the temperature of the skin can be divided into two groups—the external and the internal. Of the former, the most important are climate, which comprises temperature, moisture and wind, and clothing; of the latter, muscular work is the chief. These factors have been considered already; abnormal ones will be discussed later.

### The Regulation of Temperature.

The regulation of the temperature of the body is under the control of the central nervous system, and involves the capacity of increasing or diminishing the production and the loss of heat.

The chief sources of heat in the body are the muscles and the glands, and these organs are under the influence of the nervous system. The loss of heat occurs chiefly from the surface of the body by radiation and conduction of heat, and by evaporation of sweat; the temperature of the skin depends upon its vascularity and the secretion of sweat, and these two factors are controlled by the nervous system. The ventilation of the lungs, whereby heat is also lost, is subject to similar regulation.

The relative importance of the two methods of regulation varies in different animals; man, owing to his naked skin and the great development of his sweat-glands and vasomotor system, regulates his temperature chiefly by variations in the loss of heat. The reaction to changes of external temperature appears to be dependent chiefly upon reflex responses to the temperature of the skin. In cold weather the vessels of the skin of exposed parts are so contracted that the blood-supply is diminished, and in some areas is so sluggish that the skin is "blue with cold." The skeletal muscles are in a condition of greater tone, and muscular work is carried on energetically, or, if no work is done, the tone may become so marked that involuntary contraction or shivering arises. Shivering is a protective mechanism, and increases the combustion in some cases by 90 per cent. The constriction of the cutaneous vessels diminishes the loss of heat, and in some healthy people this vasomotor reaction may be so pronounced in the fingers that they become white and bloodless, and, in popular language, "die away with the cold"; this condition, as already mentioned, is not a sign of any disease in the heart or bloodvessels, but is due to a constriction great enough to resist the pressure of the blood, which may be low. A marked contrast is seen in hot weather; the vessels of the skin are dilated and flushed with blood, and sweat moistens the surface. The diminished tone of the voluntary muscles is shown in a languid performance of work, or the disinclination to any active movements which would increase the production of heat.

These well-known effects of heat and cold are not sufficiently borne in mind. A bracing climate is one which stimulates the body to increased activity by favouring the loss of heat; a relaxing climate depresses the body, owing to the high temperature, moisture, and absence of wind, which delay the loss of heat. The practical importance of these effects is very great, for experiments, as well as experience, prove that the effect of different climates are not due to differences in the chemical purity of the air. The air is less stagnant in the country than in the town, for the effects of wind are not reduced by long lines of lofty houses. The influence of climate upon man must be considered in relation to its effect upon the regulation of temperature. The activities of the nervous and muscular systems are increased by cold; the demands for food,

clothing, and shelter, become imperative, and these conditions favour the development of an active and intelligent race. The same principles must be borne in mind in the selection of health resorts for invalids; some require a bracing, others a relaxing atmosphere.

The perfection of the regulation of temperature in man is shown by his capacity to adapt himself to a wider range of climate than any other animal. This power is not due entirely to his greater mental development, whereby he is able to alter his clothing, food, and surroundings according to his needs, for experiments show that without resource to such aids he is able to regulate his temperature more perfectly than other animals can. Lefèvre has made interesting observations to demonstrate this. He remained for three hours in a bath at 15° (59°), and found that his axillary temperature fell only 1°—from 37·3° to 36·3° (99·14° to 97·34°)—although the amount of heat lost was 800 kilocalories. A bath of one hour's duration in water at 7° (44·6°) caused a fall in his temperature from 37·7° to 36° (99·86° to 96·8°), the loss of heat being 530 kilocalories.

The question whether the regulation of temperature depends upon special nervous centres has been the subject of numerous experiments, and of even more numerous discussions. Much of the evidence will be reviewed later, when the effects of injury of the central nervous system are considered; nevertheless, it is necessary, for the further study of the production and loss of heat, to attempt to indicate the nature of the process. In the first place, oxidation and the production of heat are fundamental characteristics of all forms of life, and loss of heat will occur, under suitable external conditions, by radiation, conduction, and evaporation of moisture. The chemical processes in the living organism are less active when its temperature falls below a certain optimum; there is, therefore, in plants and the lower animals a seasonal variation in activity, growth, and reproduction. Such a dependence upon external temperature imposes a limitation to a continuous active life, and is incompatible with the highest development found in birds, most mammals, and man.

The capacity to maintain the internal temperature near its optimum involves an active response to cold—an increased combustion or a diminished loss of heat. A response to heat is likewise necessary—an increased loss of heat or a diminished combustion. This capacity to respond with a purpose in view is not a fundamental property of the individual tissues of the warm-blooded animals, for isolated organs or tissues react in a similar way to that shown by cold-blooded animals. The response depends upon the special development of the nervous system, upon the control which it exercises over the various organs of the body. This power has been evolved, and it is possible to trace its development

in the animal series as well as in the individual warm-blooded animal, during the different stages of its life.

**The Development of the Power of Regulation.***—A consideration of the Darwinian theory of evolution leads to the conclusion that the power of regulation of bodily temperature has been acquired gradually. Experimental evidence supports this view. The embryo in the egg passes through a stage of development, during which it responds to changes in external temperature in a similar manner to that shown by a cold-blooded animal. When the chick is hatched, it can regulate its temperature; it is warm-blooded, its eyes are open, it is covered with down, and rapidly learns to feed itself and co-ordinate its movements. Birds which are naked, helpless, and blind at the time of hatching, are unable to regulate their temperature. A similar difference is seen in the young of mammals. A newly born guinea-pig, which is covered with fur and has its eyes open, is able to co-ordinate its movements and regulate its temperature; a rabbit, on the other hand, is born naked, blind, and helpless, and cannot maintain its temperature if it be exposed to moderate cold.

Hibernating mammals, such as the marmot, dormouse, bat, and hedgehog, appear to have retained characteristics of their cold-blooded ancestors. In winter they pass into a torpid condition, similar to that seen in cold-blooded animals; in summer they regulate their temperature, but not so perfectly as ordinary mammals do, for, whenever they become inactive and sleepy, their temperature is liable to a considerable decline.

The chain of evidence is completed by the monotremes and marsupials, the lowest representatives of the mammals; their temperature shows large variations, and is regulated imperfectly.

In man there is evidence of the gradual development of the power of regulation during fœtal life. The premature infant cannot regulate its temperature if it be exposed to the ordinary temperature of a room; it must be kept warm by artificial means. The lives of many such infants have been saved by the use of incubators. The child born at full time shows considerable variations in its temperature, and cannot maintain its temperature at the normal level of an adult if it be exposed to cold. As in the case of other young mammals, the infant's capacity to regulate its temperature appears to depend upon the development of the nervous control over the skeletal muscles and the bloodvessels; the stronger and more active the infant, the greater is its power of resisting the action of cold.

The practical importance of this subject lies in the treatment of infants. For their proper development, weak infants require more warmth than strong ones, and premature infants will die unless

* See "Animal Heat," *Textbook of Physiology*, edit. by Schäfer, 1898, vol. i., p. 865.

they are kept warm by artificial means. When, however, a healthy infant is several months old, it does not require artificial warmth, provided that it is fed and clothed well. A moderate degree of cold acts as a stimulus to its muscular activity and metabolism, and favours a sturdy growth; the practice of keeping an infant night and day in a room artificially warmed defeats its own aim. Resistance to the effects of changes of temperature can be acquired only by practice.

The development of the power of regulation is not accompanied by the appearance of any special structure in the animal, but is associated with the control of the nervous system over the muscles and with increased sensibility; the sensation of cold causes increased tone of all the muscles, those of the bloodvessels included; the sensation of heat produces relaxation of the muscles. Thus, in the first case, more heat is produced and less lost, and in the second case the effects are reversed.

**The Regulation of the Production of Heat.**—The two chief sources of heat in the body are the muscles and the glands. The former make up almost 50 per cent. of the weight of the body, the latter only 3 or 4 per cent. The activity of the muscles is accompanied by the production of heat; and even rest is a condition of slight activity, for the muscles are in a partly contracted state, a condition known as "tone." It has been shown already how muscular activity is the chief factor in the causation of the daily variation in temperature, and it is known to everyone that muscular work brings a sensation of warmth. During exercise the internal temperature of a healthy man may be raised to 38·9° (102°) or even higher, notwithstanding the increased loss of heat. Direct experiments have proved that a muscle is warmer than its arterial blood, and gives up heat to the blood which circulates between its fibres. The glands of the body are the second important source of heat. The liver of an adult man weighs 3 to 4 pounds (1,363 to 1,818 grammes), and is active even when digestion is not in progress. The kidneys, each of which weighs about 5 ounces (142 grammes), are constantly in action, and the urine leaving them may be warmer than the aortic blood. The digestive glands show periods of activity and of rest, and doubtless contribute to the production of heat.

The actual production of heat in a man's body is not determined easily; a large calorimeter, or, better, a combined calorimeter and respiration chamber, is required, and such apparatus for exact observations demands a large expenditure of money, time, and skill. The most important work upon this subject has been carried out by Atwater and Benedict.* They determined not only the

* *A Respiration Calorimeter*, Washington, 1905. Benedict and Milner, *Experiments on the Metabolism of Matter and Energy in the Human Body*, Washington, 1907.

production and loss of heat, but also the total metabolism of men under various conditions of fasting, feeding, and work. Their observations confirm the earlier ones of Rubner, who showed that in the living body the law of the conservation of energy holds good, and that it is possible to calculate the production of heat in the body from the caloric value of the food consumed. For clinical purposes, such a calculation is of great value ; a patient's intake of food, excreta, deep and surface temperature, loss or gain in weight, can be determined, and from these data an estimation of his production and loss of heat can be made.

The discharge of carbon dioxide from the body can be measured, but no correct estimate of the production of heat can be obtained thereby. When, however, both the output of carbon dioxide and the intake of oxygen are determined, it is possible, from the respiratory quotient, to draw conclusions as to the nature of the food material which is undergoing oxidation within the body, and to calculate the production of heat. A general idea of these relationships will be obtained from the following table prepared by Benedict and Joslin* :

RESPIRATORY QUOTIENTS AND CALORIFIC EQUIVALENTS OF CARBON DIOXIDE AND OXYGEN FOR PROTEIN, FATS, AND CARBOHYDRATES OXIDIZED IN THE BODY.

| Materials. | Oxygen required to Oxidize One Gramme. | | Production of the Oxidation of One Gramme. | | | | Respiratory Quotient: $\frac{CO_2 \text{ c.c.}}{O_2 \text{ c.c.}}$ | Calorific Equivalent of One Gramme of— | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Carbon Dioxide. | | Water. | Heat. | | Carbon Dioxide produced. | Oxygen required. |
| | Weight. | Volume. | Weight. | Volume. | | | | | |
| | Grms. | C.C. | Grms. | C.C. | Grms. | Cals. | | Cals. | Cals. |
| Starch .. | 1·185 | 829·5 | 1·629 | 829·3 | 0·556 | 4·20 | 1·000 | 2·58 | 3·55 |
| Cane sugar | 1·122 | 785·4 | 1·543 | 785·5 | 0·579 | 3·96 | 1·000 | 2·56 | 3·53 |
| Glucose .. | 1·066 | 746·2 | 1·466 | 746·2 | 0·600 | 3·75 | 1·000 | 2·56 | 3·52 |
| Animal fat | 2·876 | 2013·2 | 2·811 | 1431·1 | 1·065 | 9·50 | 0·711 | 3·38 | 3·30 |
| Human fat | 2·844 | 1990·8 | 2·790 | 1420·4 | 1·055 | 9·54 | 0·713 | 3·42 | 3·36 |
| Protein .. | 1·367 | 956·9 | 1·520 | 773·8 | 0·340 | 4·40 | 0·809 | 2·90 | 3·22 |

The production of heat is raised by muscular work and by food. The following figures represent the energy value of the diets† of men doing different amounts of work and receiving sufficient food for their needs :

* *Metabolism in Diabetes Mellitus*, Carnegie, Institution of Washington, 1910, p. 166.

† See also p. 609.

| | Protein. | Fat. | Carbo-hydrate. | Calories. | Remarks. |
|---|---|---|---|---|---|
| | Grms. | Grms. | Grms. | | |
| *Atwater's Standards* — No work .. | 100 | — | — | 2,700 | Definite amounts of fat and of carbohydrate are not given, but they must be sufficient to make up with the protein the number of calories. The standards are for food actually eaten. |
| *Atwater's Standards* — Light work .. | 110 | — | — | 3,000 | |
| *Atwater's Standards* — Moderate work | 125 | — | — | 3,500 | |
| *Atwater's Standards* — Hard work .. | 150 | — | — | 4,500 | |
| *Atwater's Standards* — Very hard work | 175 | — | — | 5,500 | |
| Average food supplied gratis to four British regiments .. .. | 133 | 115 | 424 | 3,369 | Waste included, but not extra food bought. |
| Russian Army war ration (Manchuria) | 187 | 27 | 775 | 4,891 | — |
| Japanese Army war ration (Manchuria) | 158 | 27 | 840 | 4,343 | — |
| Members of two college football teams, United States of America .. .. | 225 | 334 | 633 | 6,812 | Food eaten. |

Researches made upon man indicate that there is a certain optimum temperature of the air at which the output of carbon dioxide is at its minimum ; this is illustrated by the following figures* :

| | | | | | |
|---|---|---|---|---|---|
| Temperature of air .. .. | 14° | 16·6° | 18·1° | 21·9° | 25·2° |
| Output of carbon dioxide (in grammes per hour) .. .. | 41·5 | 36·1 | 26·9 | 28·4 | 32·7 |

Under the ordinary conditions of active life a cold external temperature increases the appetite and the capacity for muscular work, and thus the production of heat is maintained at a higher level. A patient kept warm in bed does not need to produce much heat, and has, in most cases, a poor appetite for food ; there is, indeed, evidence to show that the value of rest in bed is overestimated by many medical men, especially in the case of patients in hospitals and infirmaries, where less trouble is given to the nursing staff, and discipline is more easily maintained by keeping patients in bed.

An adult man produces about 1,700 calories in twenty-four hours when he is fasting and remains perfectly quiet in bed. The sources of this heat have been calculated. The heart, during its work, produces about 70 calories, and the respiratory muscles about 150 calories ; the heat due to the activity of the liver and kidneys has been estimated by Tigerstedt at 368 and 74 calories respectively. The sum of these is 662 calories, so that there remains a balance of about 1,000 calories, which must be formed almost entirely in the skeletal muscles. The minimum production of heat in twenty-four hours by a man weighing 70 kilogrammes

* See Tigerstedt, *loc. cit.*, s. 594.

(11 stone) may be estimated at 1,200 calories arising from the muscles, and 500 calories from the glands.

**The Regulation of the Loss of Heat.**—It has been stated already that man regulates his loss of heat by radiation and conduction, and by the evaporation of moisture from the lungs and the skin. The relative importance of these losses must be considered. Atwater gives as the result of his calorimetric observations upon man the following values for the loss of heat during twenty-four hours :

| | Man at Rest. | Man at Work. |
|---|---|---|
| | Calories. | Calories. |
| Radiation and conduction .. .. .. .. | 1,683 | 3,340 |
| Urine and fæces .. .. .. .. .. | 31 | 26 |
| Evaporation of moisture from lungs and skin .. | 548 | 859 |
| | 2,262 | 4,225 |

In the above table the loss of heat by the evaporation of moisture is given in one figure, for Atwater did not make separate determinations of the moisture discharged from the skin and from the lungs. Tigerstedt has calculated that the loss during rest would be proportioned as follows : 306 calories for the lungs, and 242 calories for the skin.

The loss of moisture from the skin* by the process of perspiration increases with the external temperature, but if the man be at rest and not exposed to a high temperature, there is no discharge of sweat. Directly, however, the external temperature reaches the critical point, between 33° and 36° (91·4° and 96·8°), beads of sweat appear, and there is a great increase in the discharge of water and carbon dioxide from the skin. This is proved from the results of Schierbeck's observations upon a man clothed, but at rest :

| Temperature of Air. | Water from Skin per Hour. | Carbon Dioxide from Skin per Hour. |
|---|---|---|
| | Grms. | Grms. |
| 28·4° | 51·0 | 0·35 |
| 28·9° | 50·8 | 0·33 |
| 29·5° | 74·3 | 0·33 |
| 31·8° | 110·1 | 0·30 |
| 32·7° | 119·1 | 0·37 |
| 33·4° | 122·3 | 0·80 |

The great increase in the discharge of carbon dioxide from the skin when the temperature of the air rose to 33° (91·4°) indicates

* For further details and references see "The Functions of the Skin," *Brit. Journ. Dermatology*, 1910.

the point at which sweating began. The discharge of water from the clothed skin when the temperature of the air was 32° (89·6°) was equal to that from the naked skin at a higher temperature—namely, 36° (96·8°); in the former case sweating was absent, in the latter it was present.

The clothed condition is the natural one for all but those who live in tropical climates, and it is necessary to consider the discharge of moisture from the skin at the temperature of the air which is confined in the clothes. That temperature is about 32° (89·6°) under the ordinary conditions of external temperature, and therefore we may estimate the loss of moisture from the skin of a man clothed and at rest to be between 2,000 and 3,000 c.c. in twenty-four hours. These values are for the losses by perspiration alone. When the sweat-glands become active, owing to a higher temperature or to muscular exercise, the losses are very much greater. A man may lose as much water during one hour of active exercise as he would lose in twenty-four hours of rest.

A distinction has been drawn between perspiration and sweating, and more evidence must be given in support of the contention that these are two distinct processes. Some observers have maintained that only one process is concerned, and their view is reflected in the common use of the word "perspiration" in the sense of sweat. The evidence, however, is against that view. The discharge of moisture from the skin of a man at rest, and not exposed to a high temperature, is proportional to the temperature; it is greater if the air be dry, and less if the air be stagnant; it is diminished if the surface of the skin be covered with fat. These are variations which would be expected in a transudation. Directly, however, the temperature of the air reaches a sufficient height, a new process appears to come into play; beads of sweat appear, and there is a great increase in the discharge of carbon dioxide from the skin. Perspiration appears to be a transudation influenced chiefly by the vascularity and temperature of the skin; sweating is an active secretory process controlled by the nervous system. It is well known that a secretion of sweat may be evoked by emotions. Fear and pain will produce profuse sweating in man, and stimulation of most afferent nerves will evoke a secretion by reflex action. Further evidence of the influence of the nervous system upon the sweat-glands will be given later in connection with disordered regulation of temperature.

The influence of other factors upon the secretion of sweat must be considered. In the first place, the relation of the blood-supply is the most important; the general condition is that sweating is accompanied by a dilatation of the bloodvessels of the skin. This is the healthy reaction to increased heat, for the loss of heat from the skin is increased thereby. The composition of the blood has a marked effect upon sweating; an accumulation of carbon dioxide

or a decrease in the oxygen of the blood will produce sweating. A rise in the temperature of the blood affects not only the nervous centres, but also the excitability of the sweat-glands. In short, the conditions which accompany muscular work and raise the temperature of the body are those which stimulate the secretion.

In the regulation of the loss of heat, sweat plays a most important part. When the temperature of the body rises owing to muscular work or to exposure to a hot atmosphere, the loss of heat is increased by the cooling effect of the evaporation of the sweat which is poured out from the orifices of the numerous glands. It is owing to the evaporation of sweat that it is possible for a man to remain exposed to a dry heat many degrees above the temperature of his body. Benjamin Franklin observed during the hot weather at Philadelphia, in 1750, that his temperature remained normal, although the external temperature was 37·8° (100·04°) in the shade; this result he attributed to the cooling effect of the evaporation of sweat. This explanation was proved to be correct by Blagden and Fordyce during their experiments upon the effect of extreme heat upon man. They remained for fifteen minutes in a dry room which was heated to 126° (226·44°), and found that their temperatures did not rise above the normal, although the room was so hot that beef-steaks were cooked by the heat of the air. Into the heated room two jars of water were brought, and a layer of oil was placed on the surface of the water in one, with the result that the water quickly boiled, owing to the absence of evaporation; on the other hand, the water in the other jar rose to 60° (172°), but did not boil, evaporation taking place freely from the surface, and thus cooling the water. In such hot atmospheres the loss of heat by radiation and conduction has ceased, and the temperature of a man would rise if the evaporation of sweat did not cool the surface of his body. If the air is moist as well as hot, the evaporation of sweat cannot proceed rapidly enough to prevent the temperature of the body from rising.

Nothing demonstrates more clearly this function of the sweat than the effect of absence of sweating when the heat of the body is increased. Zuntz* and Tendlau made observations upon a man whose skin was devoid of sweat-glands. His temperature rose to 39° (102·2°) when he was exposed to the heat of the sun in summer, or when he did muscular work for a short time. The bloodvessels of his skin were dilated in a normal manner, but radiation and conduction were not sufficient to prevent his temperature from rising when he worked. He overcame the serious difficulty caused by the absence of sweat by frequently soaking his shirt in water; the evaporation of the water cooled his skin.

The loss of heat from the skin varies greatly according to external and internal conditions. The most important external factors are

* Zuntz und Schumburg, *Studien zu einer Physiologie des Marsches*, Berlin, 1901, s. 311.

wind, temperature, and moisture. The influence of wind is well known. It is only necessary to recall the unpleasant sensation of cold experienced during a north or north-east wind, with a temperature several degrees above the freezing-point, and to contrast it with the comfort felt on a calm day with the thermometer registering ten degrees of frost. The sailors of Parry's Expedition to the Polar Seas found that they could bear more easily a temperature of $-40°$ (40°) when the air was perfectly calm, than a temperature of $-12°$ (10·4°) when there was a wind. The more stationary the air is, the less the loss of heat, for the body becomes surrounded by a layer of air with a temperature intermediate between that of the body and that of the atmosphere.

Moist air is a better conductor than dry air, and increases the loss of heat by conduction and radiation, but it does not favour the evaporation of moisture from the body. When the air is warm and dry, evaporation is rapid, but not when the air is moist. Experience supports these arguments: the sensation of cold is much greater on a cold damp day than on a dry day of the same intensity of cold as recorded by a thermometer; the discomfort in a warm, moist atmosphere is known to be far greater than that experienced on a dry day, when the thermometer is standing at a similar high level. These facts show the importance of studying the records of the wet-bulb thermometer when the climate of any health resort is under consideration; the records of the dry-bulb thermometer may give an altogether wrong impression.

During exercise in warm weather, the chief loss of heat—even as much as 90 per cent. of the total loss—may be due to the evaporation of sweat. As a practical illustration may be given the comparison of the results obtained upon soldiers when they performed a march of seven miles on hot and cold days, with the same clothing, equipment, and load (see table on p. 528). These figures show, moreover, how important a supply of water is for the efficiency of men marching on a hot day, for sweating cannot continue if the reserves of water in the body are not maintained.

### Disordered Regulation of Temperature.

The regulation of temperature may be disordered by exposure to extreme heat or cold, by injury, especially to the nervous system, and by disease; the disorder may be indicated by an abnormal rise or by a fall in temperature. The loss of heat, the production of heat, or even both of these processes, may be affected, and the temperature of the body will be the resultant of these alterations. A rise in temperature may be due to increased production, or to diminished loss of heat, or to any combination of these, provided that the production is greater than the loss. Likewise, a fall in bodily temperature may be caused by a decreased production or by an increased

loss, or by any combination of these, provided that the loss exceeds the production.

The simplest cases of disordered temperature are those in which men have been exposed, under unfavourable conditions, to extreme heat and cold, and have been unable to regulate their temperature.

| | Four Men on Hot Day. | Four Men on Cold Day. |
|---|---|---|
| Increase in pulse per minute: | | |
| Maximum | 84 | 24 |
| Minimum | 52 | 8 |
| Average | 62 | 14 |
| Increase in rectal temperature (Fahrenheit): | | |
| Maximum | 2·3° | 1·6° |
| Minimum | 0·6° | 0·0° |
| Average | 1·4° | 0·8° |
| Loss of moisture from body in grammes: | | |
| Maximum | 2,390 | 555 |
| Minimum | 1,140 | 300 |
| Average | 1,816 | 419 |
| Increase in weight of clothes in grammes: | | |
| Maximum | 640 | 40 |
| Minimum | 60 | 0 |
| Average | 320 | 27 |
| External temperature (Fahrenheit): | | |
| Dry-bulb | 79° | 45° |
| Wet-bulb | 67·5° | 38° |

**Death from Exposure to Heat: Heatstroke, Sunstroke, Heat Apoplexy.**—The cases of death from exposure to heat have been so numerous that much attention has been given to the subject, and very divergent opinions have been expressed regarding the pathology. Some authors have maintained that the disorder is not always due to the heat, but in some instances to the actinic or other rays of the sun. They have drawn, therefore, a distinction between "heatstroke" and "sunstroke." Others have suggested that the condition is due to a specific micro-organism, and is a fever which is endemic in certain hot countries. There is no evidence for the last of these views, but it is quite possible that some cases of specific fevers have been mistaken for "heatstroke," and some cases of "heatstroke" have been diagnosed as specific fevers. Experiments upon soldiers* with clothing especially designed to prevent the penetration of the actinic rays of the sun lend no support to the theory of "sunstroke" in the strict sense of the term.

* *Journ. Royal Army Medical Corps*, 1911, vol. xvi., p. 109.

A large body of evidence has been collected to show that "heatstroke" is due to a disorder of the regulation of temperature produced by the action of moist heat upon men working hard and unsuitably clothed. Muscular work increases the production of heat, and even under favourable conditions may raise the internal temperature to 101° or 102° F. If the man be exposed to a high external temperature when the air is moist and stagnant, his capacity to regulate his temperature may be easily overtaxed, if he is working hard and is unsuitably clothed or laden.* The loss of heat from the body by radiation and conduction will cease when the temperature of the external air is higher than that of the body, and if the air is very moist and not in motion it will be difficult for the man to compensate by sweating. The loss of water from the skin may be so great that the clothes are wet with sweat, but if evaporation be prevented or slow the body will not be cooled. When the temperature of the body rises, the production of heat is increased, and thus a so-called "vicious circle" arises, and will end in death unless the temperature be lowered.

Soldiers have been especially liable to "heatstroke," and many lives have been lost during forced marches, when the air was hot, moist, and stagnant. The conditions under which soldiers work are the most favourable for the production of "heatstroke"; they are unsuitably clothed, heavily laden, and march in such close order that they are surrounded by air saturated with moisture from the sweat and breath of their comrades. They march under orders, and are not free to obey the dictates of their own sensations; moreover, their pride will often make them persist in their efforts to keep up with their more efficient comrades until they fall out of the ranks and become unconscious.

Some men are more liable than others to the effect of moist heat. A good heart and vasomotor control are necessary for the flushing of the skin and the maintenance of an efficient pressure of blood. Some men do not sweat readily even when their temperature rises to a dangerous height. In fact, some patients with "heatstroke" have a skin hot and burning to the touch, but quite dry; their bodies are abnormally heated throughout all parts. In other cases, which have been described as "heat exhaustion," the skin may be bathed with sweat, and the patient in a condition of collapse, although his internal temperature is not very high. In such cases the failure of regulation appears to be due to a weak heart and defective vasomotor control. It is not easy to say whether the cardiac condition is the cause or the effect of the failure to regulate the temperature. It is well known that men with weak or diseased hearts easily fall victims to "heatstroke"; on the other hand, the heart is readily injured by a high temperature and a deficient or defective supply of blood.

* See p. 505.

That such is the pathology of "heatstroke" is borne out by the means taken for its prevention or cure. Light, loose clothing which favours the evaporation of sweat, frequent halts, and a good supply of water for drinking, will enable men to perform safely a march which would otherwise result in disaster. The most common and most successful treatment of "heatstroke" is the internal and external application of cold water or ice. The brain is the part which regulates the temperature and is most affected, and in slight cases the cooling by water or ice of the head and of the blood passing up the neck to the brain may be attended with prompt effect. In severe cases it may not be sufficient to apply the water or ice to the surface of the body, for the circulation of the blood may be too feeble to exchange the cooler blood of the surface for the hot blood of the internal parts. This will explain why ice-water enemata have been used with so much success in severe cases.

In the fatal cases the cause of death appears to be found in the effect of the high temperature upon the nervous system and heart. Well-marked changes are present in Nissl's granules and in the nuclei of the nerve cells of the central nervous system.* The globulin of the cells will coagulate at 42° if that temperature be maintained for some time.† It has been suggested that the high temperature may damage also the voluntary and cardiac muscle fibres by partial coagulation of their proteins, and thus assist in the production of cardiac and respiratory failure. Death, however, may occur at a later stage, after the hyperthermia has disappeared; in such a case it is possible that poisonous products have been produced, and accentuate by their action the damage already present in the central nervous system. Even in cases of recovery from "heatstroke," abnormal nervous symptoms may be present for years after the stroke.

**Death from Exposure to Cold.**—Healthy men and animals may die from exposure to extreme cold, especially if they have been exhausted by muscular work and deprivation of food. In popular language, they are said to be "frozen to death." It is true that the body may be frozen stiff, but death occurs long before this condition is reached. Man and other warm-blooded animals become unconscious and die when their internal temperature falls to about 20° (68°). Even in this country such cases occur from exposure. A man loses his way in the snow, and continues to trudge along until, overcome by fatigue and weariness, he surrenders to an overpowering desire to sleep. During the unconsciousness of his deep sleep his capacity to regulate his temperature is diminished, he loses much heat but produces little, his temperature steadily falls,

* Marinesco, *Revue Neurologique*, 1899; Scagliosi, *Arch. f. path. Anat. u. Physiol. u. klin. Med.*, Bd. clxv., 1901, s. 15.

† Halliburton and Mott, *Arch. of Neurology*, vol. ii., 1903.

the sleep becomes a deep coma, and he dies. Such an accident is especially liable to occur in men who are under the influence of alcohol.*

There has been considerable discussion as to the exact method whereby death is brought about in such cases. Some authors have sought refuge in the vague term "shock"; others have maintained that asphyxia is the cause. It is not easy to obtain reliable observations upon man, but the evidence yielded by experiments upon warm-blooded animals points to a progressive decline in the production of heat until the chemical processes are reduced to such a low level that consciousness is lost; the animal quickly loses its nervous control of the temperature of its body, and further exposure to cold results in a reduction of the metabolic processes to a point incompatible with life.

**Lesions of the Nervous System.**—It has been shown already how complex is the regulation of the temperature of the body; the adjustment of a balance between the production and the loss of heat involves most of the organs of the body. The production of heat is bound up with the activity of the muscles and of their glands, and this in turn demands an efficient supply of blood laden with food-material and oxygen, and purified by glands which remove poisonous products or supply the necessary internal secretions. The loss of heat is effected by the adjustment of the circulation by the vaso-motor system, by the excretion of the sweat-glands, and by the ventilation of the lungs. These several processes interact the one upon the other, and are controlled by different parts of the nervous system. It is improbable, therefore, that the belief in a special "heat centre or centres" in the brain is well founded. The fact that a lesion of one part of the central nervous system will disturb the temperature of the body is no proof that the part is a "heat centre," for the different neurones act and react upon one another, influence the various organs of the body, and are in turn influenced by them. The body works as a whole. Little has been gained from the theories of specific heat centres. No doubt some parts of the nervous system are more important than others in the regulation of the temperature of the body. The muscles are the chief seat of the production of heat, and it is to be expected that any lesion which disturbs the control exerted over them by the nervous system will disorder the production of heat. The tone of the muscles is influenced, especially in man, by the sensations of heat and cold which arise in the skin. For this reason injury to sensory pathways may cause a disorder in the regulation of temperature. The glandular activity of the body is another source of heat, and is under nervous control. The loss of heat from the body is adjusted through the influence of the nervous system upon the heart, bloodvessels, sweat-glands, and respiration.

* See p. 534.

For these various reasons we must be prepared to find that lesions of the nervous system may in some cases produce a rise of temperature, in others a fall, and in others no effect. Either production or loss of heat may be especially affected, or both may be disturbed so that the resultant temperature does not rise above the normal. If we bear in mind the facts that are known, and dismiss all the theories of special heat centres, it will be easier to understand in some measure the conditions which arise after nervous lesions in different parts and of different severity.

When the nerve-supply, both motor and sensory, is cut off from a limb, the temperature of the paralyzed areas of skin may rise above that of the corresponding parts of the intact limb, for the vasomotor tone is lost; more blood can circulate through the dilated vessels, and sweating in the case of man ceases in the paralyzed parts. In a few days a change occurs: the paralyzed limb becomes colder than the healthy one; the bloodvessels, in virtue of their local tone, have contracted, and less blood passes through the limb; the voluntary muscles have lost their tone, and their production of heat is diminished; they cease to contract, and thus the circulation of the blood loses one of the factors which favours its flow through the limb.

In paraplegia resulting from traumatic section of the spinal cord the conditions are similar; but since many more muscles are concerned, an effect may be produced upon the general temperature of the body as well as upon that of the paralyzed parts. If the lesion is low down in the lumbar region, no marked effect may be observed upon the internal temperature when the patient is kept in bed. When, however, the lesion is high up in the cord, the general disturbance of the temperature may be the chief cause of death, for the patient has lost his power of regulation. Death may be accompanied by a high or by a low temperature. The following table gives examples *:

| Sex and Age. | Seat of Injury. | Temperature. | Remarks. | Observer. |
|---|---|---|---|---|
| M. | Crush at level of fifth and sixth cervical vertebræ. | 43·9° (111·0°) between scrotum and thigh. | Diaphragmatic respiration; slow and irregular breathing; weak pulse; livid countenance; death twenty-four hours after accident. | Brodie. |
| M., 22. | Crush between sixth and seventh cervical vertebræ. | 33·9° (93·0°) on admission; 27·8° (82·0°) a few hours before death. | Patient drowsy and prostrate; death about forty-eight hours after accident. | Le Gros Clerke. |

* See also Gardiner and Pembrey, *Guy's Hospital Reports*, 1912.

The explanation of these differences appears to be found in the loss of the power of regulation. The subnormal temperature is due to an excessive loss and a diminished production of heat, owing to the vasomotor and general muscular paralysis. When a patient in such a condition is exposed to moderate cold his temperature falls. On the other hand, owing to the fact that the production of heat rises and falls in the paralyzed man *with* the external temperature, a condition of hyperthermia may result if the weather be hot and the patient covered too much with bedclothes; his temperature rises, and may reach a dangerous height, owing to the diminished loss and the increased production of heat. Below the lesion he cannot sweat, and he cannot ventilate his lungs perfectly, for, owing to the paralysis, his respiration is hampered. His normal responses to heat and cold are limited to the parts of his body which are not paralyzed: if he feels too hot, he can dilate his cutaneous blood-vessels, and sweat on only those parts of the skin; should he feel cold, he can contract his superficial blood vessels, and shiver in only the same regions. It follows also from this explanation that the opposite tendencies may counteract one another, and the internal temperature show no marked change.

The influence of the brain upon the regulation of temperature has been the subject of many experiments and clinical observations. The results are discordant, and naturally so, for the conditions are very complex. Damage to the cortex of the brain may cause either a rise or a fall or no definite change in the temperature of the body; the determining factor appears to be the extent to which the motor and sensory nerves, concerned in the tone of the skeletal muscles and the involuntary muscles, are involved. Puncture or lesions of various parts of the brain, especially in the region of the corpus striatum and optic thalamus, may cause a rise of temperature or hyperthermia. The general result is an increase in the production of heat, apparently due to an increased combustion in the liver and muscles. The nervous regulation of temperature is disturbed; the puncture may have either an augmentor or an inhibitory effect upon the incoming and outgoing nervous impulses, which are concerned in the reception of sensations of heat or cold and in the co-ordination of the activity of the various organs of the body, especially the skeletal muscles and the muscles of the blood vessels.

In the celebrated experiments made by Goltz* to investigate the effects of removal of the cerebrum in dogs, it was found that the dog without a cerebrum was able to regulate its temperature in a similar way to that of a normal dog, but its capacity was more limited. It experienced sensations of heat and cold and responded appropriately, but it could not maintain its temperature if it was left for long in a cold room. There was no evidence of the loss of any special centres for the regulation of the production or loss of heat.

* *Arch. f. d. ges. Physiol.*, 1892, Bd. li., s. 570.

In man injury to the cerebrum may cause considerable disturbance in the regulation of the temperature. The following are some examples of cases collected by Hale White*: Traumatic damage to the cortex of the brain, temperatures of 42·8° (109°) and 41·7° (107°); hæmorrhage into the corpus striatum, 42·2° (108°); tumour pressing on the right crus cerebri, 41·9° (107·4°).

If the explanation offered above be correct, one would expect to find that there may be a rise or a fall in the temperature of patients suffering from injury or hæmorrhage into the crura cerebri and pons. Such is the case, as shown by the following examples collected from the records of Guy's Hospital by H. L. Attwater†:

| Case. | Size and Position of Pontine Hæmorrhage. | Temperature. | Remarks. |
|---|---|---|---|
| 62 | Mid-pontine | 42·2° (108°) | Spasticity present. |
| 55 | Large pontine | 41·2° (106·2°) | Spasticity present; constant movements. |
| 30 | Two small lesions | 35·2° (95·4°) | Slight spasticity. |
| 27 | Small right | below 35° (95°) | Spasticity present. |

There is no satisfactory evidence of the existence of special "heat centres," and in the present condition of knowledge upon this difficult subject it is better for the physiologist and clinician to observe the effects of lesions of the nervous system, with especial reference to the sensory, motor, and secretory disturbances which may be produced.

**The Action of Drugs.**‡—The temperature of the body may be raised or lowered by the action of drugs. For this reason two groups of drugs—the pyretics and the antipyretics—have been distinguished. Such a classification may be useful, but it is not exact, for the same drug may act as either an antipyretic or a pyretic according to the dose or the stage of action. The term "pyretic" is undesirable also on the ground that it suggests that the drug produces fever.§

Many drugs have a profound action upon the nervous system; some produce excitation, others depression. It is not difficult, therefore, to understand that the regulation of temperature may be disturbed as a part of the general disorder, and nothing is to be gained by statements that the drug acts upon special centres for the control of the production or the loss of heat.

Alcohol produces a fall in temperature, and not an increased heat of the body. The popular idea that it "keeps out the cold" and

* *Brit. Med. Journ.*, 1894, vol. ii., p. 1093.

† *Guy's Hospital Reports*, 1911, vol. lxv., p. 339.

‡ See Loewi, "Pharmakologie des Wärmehaushalts," *Ergebnisse d. Physiol.*, 3ter Jahr, Abt. i., 1904, s. 332. Here a list of 169 papers is given.

§ See p. 537.

warms the body is erroneous, and is due to the fact that there is a feeling of increased warmth after drinking alcohol. Sensations of heat or cold arise in the skin, and alcohol increases the vascularity of the skin and the activity of the sweat-glands. The loss of heat is increased, and the normal reaction to cold—namely, increased production of heat and contraction of the cutaneous bloodvessels—is blunted, or even paralyzed, by large doses of alcohol. Some of the lowest temperatures have been recorded in the case of drunkards exposed to cold; men with rectal temperatures as low as 24° (75·2°) have recovered under careful treatment and nursing. Although this is the general effect of alcohol, it is possible for the disordered regulation produced by frequent drinking to exhibit itself as a high temperature when the man is obliged to work under adverse external conditions, such as a hot and moist atmosphere. Alcohol is thus a factor which enters into the causation of some cases of heatstroke.

Caffeine, atropine, and cocaine, raise the temperature of animals. The excitability of the central nervous system is altered, the tone of the muscles and their production of heat is increased, and in some cases the loss of heat is diminished by the contraction of the cutaneous bloodvessels. Poisonous doses of tetrahydro-β-naphthylamine may raise the temperature of rabbits as high as 44·3° (111·8°); the excitability is increased, the muscles, especially those of the hind-limbs, show forcible spasmodic contractions, and convulsions may follow; the absorption of oxygen and the output of carbon dioxide* are increased, a trustworthy sign of an increased production of heat.

The general effect of anæsthetics, such as chloroform, ether, chloral, and morphia, is to cause a fall in the temperature of the body. The sensations of heat and cold are absent, and the muscles are paralyzed. In this way poisonous doses so greatly depress the power of regulation that a warm-blooded animal passes into a condition in which it cannot maintain its temperature; it resembles a cold-blooded animal, its respiratory exchange and temperature varying with, and in the same direction as, that of its surroundings. A similar effect can be produced on man by long and deep anæsthesia, and surgeons have found by experience the necessity of artificial warmth for patients deeply anæsthetized during a long operation.

Animal extracts have in many cases a poisonous effect upon the body, and the temperature may be raised during the process of the formation of antibodies. An effusion of blood may cause a rise of temperature even when there are no signs of the presence of micro-organisms; this appears to be due to the absorption of the products formed during coagulation and hæmolysis. The administration of thyroid extract will produce a rise of temperature.

* Mutch and Pembrey, *Journ. Physiol.*, vol. xliii., 1911, p. 109.

Antipyretics have little or no effect upon the temperature of healthy men when they are given in doses which would produce a definite fall in the temperature of a patient suffering from fever; likewise the respiratory exchange and the nitrogenous metabolism generally remain unaltered in the healthy man. This difference is of interest, for it confirms the view that in fever the regulation of temperature is disordered, and not "set at a higher level," as suggested by Liebermeister.

**The Action of Micro-Organisms.**—A rise of temperature is generally a characteristic development when a man is infected with a specific disease; indeed, it will be shown later* that the type of the disturbance in the daily variation of temperature may be peculiar to the disease. The micro-organisms grow and multiply, and produce chemical substances, or toxins, which affect the body as a whole, and especially the central nervous system. The toxins produce in man and animals a disturbance in the regulation of temperature; there is generally an increased metabolism and an increased production of heat. It is possible, however, with a large dose to produce depression and a fall of temperature; this is often seen in animals. Examples of such toxins are tuberculin and diphtheria toxin. The presence of the toxins leads to the production of an antitoxin, and the process is a gradual one. The disturbance in the temperature and the metabolism must be considered as a part of the response of the protective mechanism of the organism, and it is interesting to find that a low temperature is often a bad prognostic sign in old people suffering from an infectious disease—for example, pneumonia. This subject is related so closely to fever that further details will be given under that heading.

Numerous attempts have been made to isolate the pyrogenetic substances, but the results are not very definite. The substances may be of a protein nature or derived from the breakdown of proteins; it is known that there are many products which exert a disturbing action upon the metabolism and the regulation of temperature. A febrile reaction is produced in a susceptible subject when small doses of a culture, in which the virulent bacteria have been destroyed, are injected under the skin in the process of protective inoculation.

## Fever.

Fever must be considered as a complex disorder during which the exchange of material and the regulation of temperature are disturbed. The elevation of the temperature of the body is one of the usual signs of fever, but it is not an essential one. Much confusion has arisen owing to the fact that the term "fever" has been taken as synonymous with a rise of temperature. The origin of this confusion is easy to understand directly the progress of medical

* See p. 538.

knowledge is considered. From the earliest times physicians have had forced upon their notice the abnormal heat of the body during certain diseases; their patients constantly complained of being too hot, or of "hot fits" following "cold shivers." Nothing was known then about the real nature of infectious diseases and the chemical changes which occurred in the body. The modern investigations of infection and immunity have shown that a rise of temperature is only one aspect of the complex disorder, fever, and may, indeed, be absent. The term "pyrexia" has been used to designate the high temperature, but here again confusion has arisen, for the use of the word has not been consistent. In proof of this it is only necessary to recall the use of such a contradictory term as "apyrexial pyrexia." It would be well if agreement could be reached by the restriction of the use of the word "fever" to the complex process of disordered metabolism produced by the reaction of the body to the successful invasion of micro-organisms; "pyrexia" to the rise of temperature which is so frequently a marked characteristic of such diseases; and "hyperthermia" to the high temperature produced by other causes than infection, such as lesions of the central nervous system, external heat, and the poisonous action of drugs.

**The Temperature during Fever—Pyrexia.**—The rise of temperature due to the altered regulation may vary according to the nature, severity, or stage, of the disease, and clinicians and laity alike often speak of a fever in terms of pyrexia. The following classification due to Wunderlich is given, for it is in general use. It is necessary, however, to insist that it has no exact value; the actual temperature and the part of the body in which it was observed are the data which should be given, together with the time and the day of disease.

Slight fever: 100·4° to 101·12° F. (38° to 38·4° C.).
Moderate fever: 101·3° to 102·2° (38·5° to 39°) in the morning, and rising to 103·1° (39·5°) in the evening.
Considerable fever: 103·1° (39·5°) in the morning, and 104° (40°) in the evening.
High fever: 103·1° (39·5°) in the morning, and above 104·9° (40·5°) in the evening.
Hyperpyrexia: 107·6° (42°) or more.

In the above table the use of the term "fever" is, as already mentioned, open to objection, for it there signifies a rise in temperature. The severity of a fever cannot be gauged by the thermometer alone. A patient with a high temperature may be in a far less serious condition than another patient whose temperature is lower, although both are suffering from the same infectious disease.

It is now necessary to consider in detail the temperature during the different stages of a fever due to the successful invasion of the body by pathogenetic organisms. In the *initial* stage the internal

temperature may rise slowly or rapidly, the surface temperature of the skin may fall, and the patient suffer from a *rigor*; he looks pale or dusky, he shivers and shakes and complains of feeling cold, although his internal temperature is above the normal. His complaint is well founded, for his skin is cold, as shown by its colour and temperature, and his sensations of heat and cold arise in the skin, not in the internal parts of his body. The duration of the rigor varies; it may last half an hour or an hour or two. In the initial stage of some fevers there may be no definite rigor, but a stage of depression, during which the internal temperature of the patient gradually rises above the normal.

The initial stage is succeeded by the second stage, or *fastigium*. The skin becomes flushed and hot, and the patient now complains of heat and thirst. The height of the pyrexia has been reached; its duration varies according to the nature of the disease: in ague it may last only a few hours, in typhoid fever many weeks.

The third stage, or *defervescence*, may begin suddenly, and proceed rapidly, the internal temperature falling three or four degrees Fahrenheit in a few hours, and the patient sweating profusely. This is defervescence by *crisis*, and is frequently seen in cases of pneumonia. In others the termination may be by *lysis*; the temperature falls gradually, rises again, and then falls slowly to or below the normal.

Although these three stages may be recognized in many cases of fever, it is necessary to remember that in some it may be impossible to say when the one stage ends and the other begins. This is exactly what might be expected if fever be due to the invasion of the body by a micro-organism, which has a specific effect. In different fevers there is a different pathogenetic organism, and the type of the pyrexia is often characteristic of the disease. If the curve of the temperature is not typical, it is important to remember that mixed infections occur. In pneumonia the range in the daily variation of temperature is slight—there is said to be *continuous* "*fever*" (pyrexia); in tuberculosis the variation is a degree or more, and *remittent* is the term used to describe it; in so-called *intermittent* or *recurrent* fevers there are alternating periods of subnormal and high temperatures, as in malaria and Malta fever.

The explanation of the course of the temperature in different diseases will no doubt be found in the processes of infection and immunity. Already there is evidence of a most interesting kind. In the case of malaria, Golgi discovered that the rise in the patient's temperature during an attack coincided with the segmentation and sporulation of the malarial parasite; in tertian ague the sporulation occurs every forty-eight hours, and in quartan ague every seventy-two hours. Quinine directly destroys the malarial organism and prevents the rise of temperature.

In relapsing fever there is also a relationship between the stages

of the disease and the micro-organism. In the early stage of an attack the spirilla (spirochæte or spirillum of Obermeier) are very few, but they increase in number gradually, and reach a maximum a short time before the crisis. Then they decrease rapidly, and have disappeared completely soon after the beginning of the sweating which accompanies the crisis. Antibacterial substances are produced, and check the development of the spirilla; a fresh attack appears to be due to the decrease in these protective substances.

In pneumonia the rapid fall of temperature at the crisis seems to depend upon a considerable leucocytosis and the appearance of a large amount of pneumococcus opsonin;* the pneumococci generally disappear from the blood at the beginning of the crisis. The protective substances are developed rapidly. In cholera and typhoid fever, on the other hand, the process is a more gradual one, and the pyrexia terminates by lysis.

These facts are very suggestive, and indicate the necessity of great care in the use of antipyretics. The process of fever may be an indication of a favourable development of antibodies, which may be interrupted by powerful drugs.

**The Regulation of Temperature during Fever.**—The nervous control of the production and loss of heat is altered by the poisonous action of the micro-organisms which infect the patient, and it follows, from what has been said about the regulation of temperature during health, that the disturbance may be complex and may vary. Neither increased production nor diminished loss of heat alone will explain every rise of temperature. In fever the normal balance between the two processes is altered, and pyrexia will be the result if the production be greater than the loss of heat. The relationship of these processes to each other, but not to the normal, is the important factor.

The products of the activity of specific organisms are different, and show a selective action upon the tissues of the patient. The phases of the life-history of the organism may have a relation to the varying course of the fever, as in ague, and the production of antibodies and of immunity may require different periods of time. In some such manner there arises a type of temperature which is characteristic of the disease. The daily record of the patient's temperature may be of the greatest importance in diagnosis and prognosis.

During fever the nervous control of temperature is altered, but it is not paralyzed; the patient responds appropriately to heat and cold, but he is affected more easily than the healthy man. The daily variation in temperature is present, although it may be altered in its range or in its relation to night and day. The nervous control of the fevered patient appears to be more labile, for he is affected

* Eyre, *System of Medicine*, edited by Allbutt and Rolleston, vol. v., 1909, p. 244.

readily by excitement or muscular effort. A further examination will show that the regulation of temperature during fever is affected both as regards the production and the loss of heat. In the initial stage there is increased muscular activity, the shiverings of rigor, associated with increased production of heat; contraction of the muscles of the arterioles of the skin, accompanied by diminished loss of heat and moisture. At a later stage the bloodvessels of the skin are dilated and flushed with blood, and there may be profuse sweating. The whole body is affected: the muscles waste, and there is an increased discharge of nitrogenous substances in the urine; the appetite for food and the capacity for muscular or mental work are lost. All of these factors influence the regulation of the temperature of the body, and require further consideration in relation to the production and loss of heat during fever.

**The Production of Heat during Fever.**—The difficulties in the direct determination of the production of heat in a healthy man have been mentioned already, and it is not surprising that discordant results have been obtained by those investigators who have employed imperfect methods in the determination of the heat produced by patients suffering from fever. Even with good methods the results may be discordant, for fever is such a complex process that at one time the production of heat may be increased, and at another it may be diminished. It is unnecessary to give an account of the methods and results, but there are certain indications which are of the greatest practical importance. The distribution of heat in the body of a patient can be determined from the temperatures of the mouth, axilla, groin, rectum, and skin. If these be raised above the normal, and there is no evidence of a diminished loss of heat, the production must be increased. Further evidence can be obtained by estimations of the respiratory and nitrogenous exchanges; but it is necessary to insist that the results must be compared with those yielded by a healthy individual kept in bed and fasting, or receiving only a fever diet. Food and exercise increase the exchange of material, and many fevers are accompanied by partial starvation.

The consideration of this subject is confined to the condition of fever in man for two reasons: in the first place, the physician is obliged to study man; in the second place, the great development of the vasomotor system and of the sweat-glands, and the naked condition of the skin, are so human a characteristic that it is difficult to draw from the results obtained upon animals conclusions directly applicable to man.

*The Respiratory Exchange as a Measure of the Production of Heat.*—The production of heat is due to oxidation within the tissues, and estimations of the intake of oxygen and the output of carbon dioxide afford not only a measure of this oxidation, but indicate also in the respiratory quotient the nature of the material consumed. The patient during a fever fasts or takes but little food, and thus the

substances which undergo combustion must be derived chiefly from his tissues; the muscles waste, and there is a greatly increased discharge of nitrogenous substances in the urine. The respiratory quotient is often low (0·7), and resembles that of a fasting animal. Even lower quotients have been found by careful observers, and indicate, as does the nitrogenous waste, that the processes of oxidation in a fevered patient are different both in quality and quantity from those in a healthy man.

During fever the respiratory exchange* is increased in most cases, but it is generally not above 20 per cent. of the exchange in the afebrile condition. In the early stage, as in a rigor, there is increased muscular tone, but at the same time there is a diminished loss of heat. It would appear that the explanation of the phenomena is to be found in a stimulating effect of the toxins of the micro-organisms upon the motor nervous system, including the parts which control the skeletal muscles and those of the bloodvessels and skin. The stimulation of the first is shown by the chattering of the teeth and the shivering of the patient; of the second by the pallid and cold skin; and of the third by the condition known as "goose skin."† The temperature of the surface falls, and the patient feels cold; the heat of the internal parts rises, for there is a diminished loss and an increased production of heat.

The decrease in the loss of heat may be so great that the temperature may rise even when the production, as indicated by the respiratory exchange, remains at or slightly below the normal level. During convalescence the respiratory exchange shows a considerable increase, the respiratory quotient rises, and there is a definite response to food; the patient begins to regain his flesh and fat. It is impossible, therefore, to dogmatize upon the production of heat during fever, owing to the complexity of the process and the difficulty of fixing a standard; but it may be useful to give (p. 542) a few of the results obtained by Babák and Loewy, the former with a combined respiration chamber and calorimeter, the latter with a respiratory apparatus. The examples afford valuable comparisons of the febrile and afebrile conditions in the same individuals.

**The Loss of Heat during Fever.**—It is impossible without an elaborate combination of the respiration chamber and the calorimeter to determine exactly the loss of heat from a fevered patient; and since it is unsafe to compare animals with man, owing to the naked skin and the great development of the sweat-glands of the latter, evidence must be obtained in most cases by indirect means. The investigation of the temperature of the skin during health has been considered already, and the data given will afford a standard with which to compare the conditions during fever. During the

* See Jaquet, *Ergebnisse der Physiol.*, Bd. ii., Abt. i., 1903, s. 548, where references are given.

† James Mackenzie, *Brain*, vol. xvi., 1893, p. 515.

## RESULTS OBTAINED WITH A COMBINED RESPIRATION CHAMBER AND CALORIMETER.

| Observer. | Date. | Temperature of Patient before Observation. | Temperature of Patient after Observation. | Per Kilo Body Weight and Hour. | | | | | Disease. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Oxygen absorbed, in C.C. | Carbon Dioxide discharged, in C.C. | $\frac{CO_2}{O_2}$ | Heat produced, in Kilo-Calories. | Heat lost, in Kilo-Calories. | | |
| Babák* .. | Jan. 21 | 40·5° C. | 40·5° C. | 812 | 536 | 0·66 | 3·79 | 3·79 | Broncho-pneumonia | Infant four months old. |
| | ,, 28 | 38·0° C. | 38·5° C. | 750 | 534 | 0·71 | 3·88 | 3·71 | | |
| | Feb. 12 | 37·4° C. | 37·3° C. | 912 | 692 | 0·76 | 4·82 | 4·79 | Convalescence | |
| | March 1 | 37·4° C. | 37·3° C. | 712 | 570 | 0·80 | 4·41 | 4·40 | Health | |

## RESULTS OBTAINED WITH A RESPIRATORY APPARATUS.

| Observer. | Temperature of Patient. | Volume of Air breathed per Minute, in C.C. | Carbon Dioxide per Cent. | Oxygen absorbed per Cent. | Carbon Dioxide per Minute, in C.C. | Oxygen per Minute, in C.C. | $\frac{CO_2}{O_2}$ | Nitrogen of Urine, in Grammes. | Disease. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|
| Loewy† .. | 37·7° C. | 7,624 | 2·7 | 3·7 | 207 | 281 | 0·74 | 12 | Pulmonary phthisis | Man aged 45 years; weight, 50 kilos. |
| | 40·2° C.; 39·9° C. | 7,937 | 3·5 | 3·9 | 281 | 316 | 0·88 | 17 | — | 8½ hours after injection of 8½ mg. of tuberculin. |
| Loewy .. | 37·6° C. | 7,344 | 4·1 | 4·3 | 303 | 357 | 0·85 | — | Early pulmonary phthisis | Man aged 36 years; weight, 67 kilos. |
| | 40·0° C.; 40·1° C. | 8,237 | 4·0 | 4·4 | 330 | 365 | 0·90 | — | — | 8 hours after injection of 3 mg. of tuberculin. |

* *Arch. f. d. ges. Physiol.*, 1904, Bd. cii., s. 320.

† *Arch. f. path. Anat. u. Physiol. u. f. klin. Med.*, 1891, Bd. cxxvi., s. 218.

initial stage of fever the temperature of the surface of the skin is below the normal, the bloodvessels are contracted, and the skin is cold; during the fastigium it rises, and remains above the normal even during defervescence, for the bloodvessels become flushed with blood. If, however, there is sweating, as in a crisis, the temperature of the skin falls, owing to the cooling effect of the evaporation of the moisture. The general conclusion may be drawn that at the onset of fever the loss of heat is reduced, during the progress of the fever increased, and especially so at the crisis.

Examples of the data obtained with the calorimeter have been given already.* The following† relate to the deep and surface temperature of fevered patients, and are useful as examples of the results which may be obtained readily at the bedside by the use of mercurial thermometers:

| Case. | Date and Time. | Rectum. | Mouth. | Surface. | Remarks. |
|---|---|---|---|---|---|
| | 1908. | °C. °F. | °C. °F. | °C. °F. | |
| Suppurating abdominal growth | March 25, 10.15 p.m. | 39·5 (103·2) | 39·3 (102·8) | 36·5 (97·7) | — |
| | March 26, 2.30 p.m. | 39·4 (103·0) | 39·2 (102·5) | 38·0 (100·4) | — |
| | March 27, 6.40 p.m. | 40·1 (104·2) | 38·6 (101·4) | 30·4 (86·7) | During rigor. |
| | March 27, 7.15 p.m. | 40·8 (105·4) | 38·8 (101·8) | 30·8 (87·4) | After rigor. |
| | March 28, 8.30 p.m. | 38·6 (101·4) | 38·1 (100·6) | 36·7 (98·0) | — |
| Lobar pneumonia | April 7, 6.15 p.m. | 40·7 (105·2) | — | 37·8 (100·0) | Third day. |
| | April 8, 4.35 p.m. | 40·3 (104·6) | — | 37·8 (100·0) | — |
| | April 9 .. | 38·8 (101·8) | — | 36·2 (97·1) | — |
| | April 11, 11 a.m. | 37·4 (99·4) | — | 34·5 (94·1) | 24 hours after crisis. |

The influence of the rigor and of the crisis is well shown in these cases. Further investigations, however, are necessary to determine the relation of sweating to the temperature, for there is little doubt that sweat has other functions besides that of increasing the loss of heat. Observations by Staehelin‡ upon the night-sweats of a phthisical patient indicate that a sufficient explanation of the profuse sweating cannot be found in the regulation of temperature.

**The Exchange of Material during Fever.**—The metabolism of a patient suffering from fever is characterized by an increase in the

* P. 542.

† A. S. Morton Palmer, *Proc. Physiol. Soc.*, October 17, 1908, *Journ. Physiol.*, vol. xxxvii.; *Guy's Hospital Reports*, vol. lxv., 1911, p. 103.

‡ *Zeitschr. f. klin. Med.*, Bd. lxvi., H. 3 u. 4, s. 1.

katabolic or destructive processes. The respiratory exchange is increased and the temperature is raised ; the tissues waste, and there is a greater excretion of nitrogenous substances in the urine. These are facts which can be demonstrated readily, but it is difficult to give an adequate explanation. Fever is a complex process. In the first place there is inanition, and on this account the condition of a fevered patient must be compared, not with that of a man living a normal life, but with that of a man kept in bed and fasting, or at most receiving only a fever diet. The fevered patient has no appetite, the taking, or even the sight, of food often produces nausea or vomiting, and when he can take food it is generally a starvation diet. Many of the changes in metabolism* are common to fasting and fever. The reserves of carbohydrates are the glycogen of the liver and the muscles ; these are consumed quickly. Then a drain is made upon the deposits of fat, and lastly upon the proteins of the tissues. The body wastes, the respiratory quotient falls, there is an increase in the discharge of nitrogenous substances in the urine, and a corresponding rise in the output of potassium, sulphur, and creatinin, but the amount of sodium chloride decreases.

Fever, however, is something more than inanition. The wasting is more rapid, the respiratory exchange is greater, and the excretion of nitrogen larger. The temperature is raised during fever, but not during simple inanition. This hyperthermia is another possible factor in relation to the metabolic changes. The respiratory† and nitrogenous exchanges are increased in a healthy man when his temperature is raised by hot baths or by exposure to hot air, and some observers maintain that the increase in the output of nitrogen during fever is secondary to the rise of temperature.

Another cause of increased destruction of protein appears to be the toxic action exerted upon the tissues by the fever-producing substances, for in the cachexia caused by malignant disease there is an increase in the destruction of protein, although there is no rise of temperature ; and an increase in the production of heat and the output of carbon dioxide has been found in cold-blooded animals infected with pathogenic organisms, although no rise of temperature was produced.‡

The evidence,§ although it is incomplete, justifies the conclusion that the abnormal metabolism during fever is due to several factors—the inanition, the rise in temperature, and the toxic action of the

* May, *Zeitschr. f. Biol.*, 1894, Bd. xxx., s. 1 ; Siegfried Weber, "Ueber Hungerstoffwechsel," *Ergebnisse d. Physiol.*, 1er Jahrgang, 1 Abt., 1902, s. 702 ; Lehmann, Müller, Fr. Munk, Senator, u. Zuntz., *Arch. f. path. Anat. u. Physiol. u. f. klin. Med.*, 1893, Bd. cxxxi., Suppl., s. 1.

† Sutton, *Journ. Path. and Bact.*, vol. xiii., 1909, p. 62, and references there given.

‡ Krehl u. Soetbeer, *Arch. f. exp. Path.*, 1897, Bd. xl., s. 275.

§ Graham and Poulton, *Quart. Journ. Med.*, 1912, vol. vi., p. 82, and references there given.

fever-producing substances. Yet another factor—a want of a due supply of oxygen—may cause an increased waste of the tissues when the circulation of the blood fails to meet the abnormal demands made upon it.

There is little doubt that underlying all these conditions there is the action of the enzymes, which are found in the tissues of the body, but of their relationship to the metabolic changes during fever little is known.

The examination of the urine indicates the changes in the metabolism, but gives little guidance as to the nature of the chemical processes involved during fever. The quality and quantity of the end-products show that the endogenous metabolism is increased, and this is confirmed by the obvious wasting of the tissues. The increased nitrogenous discharge begins generally after the rise in the patient's temperature, and often reaches its maximum before the temperature returns to the normal. In some cases, however, there is a great increase in the output after the crisis; this is not due, it would appear, to a retention of some of the products of the destruction of tissue during the pyrexia, for analyses of the tissues of patients who have died during pyrexia show no excess of urea. Failure of the kidneys to excrete urea does not seem to be a cause, for when that substance is given to fevered animals it is excreted readily. The explanation may be that in the process of recovery damaged tissues are removed.

**The Effect of Fever on Secretion and Excretion.**—During fever there are changes in the activity of the various glands of the body; the general characteristic is diminished or suspended activity. There is diminished secretion from the salivary glands; the mouth is dry, but this appears to be due partly to the increased loss of moisture produced by the high temperature and by breathing through the mouth. The gastric secretions are diminished, and free hydrochloric acid is often absent. These disturbances may be due directly or indirectly to the toxic action of the fever-producing substances. There is a marked loss of appetite during fever, and in the absence of that psychical stimulus to the digestive glands there will be, as Pawlow's work shows, but little secretion. Loss of appetite leads to inanition, which in turn may reduce still further the activity of these glands, for the experience of fasting men shows that, after the pangs of hunger during the first day or two, there is little or no craving for food.

The secretion of bile has been observed to be decreased during fever in a patient with a biliary fistula, and further evidence of the disturbance of the functions of this gland is found in the presence of abnormal pigments in the urine.

The activity of the kidneys* during fever has been the subject of

* For original observations and literature of the subject the following should be consulted: Garratt, *Med. Clin. Trans.*, 1904, vol. lxxxvii., p. 163.

many observations, but the results require a careful and critical examination; the quantity and quality of the various constituents must be considered in relation to the complex changes which accompany fever. It is forgotten in many cases that there is a correlation between the sweat-glands and the kidneys, and that during fever more water may be lost by means of the lungs; furthermore, the quantity and nature of the solids in solution in the urine must be compared with those in the urine of a healthy man taking only a fever diet.

During the period of incubation and the rigor there is often diuresis, due apparently to two causes—the rise of blood-pressure produced by the constriction of the cutaneous arterioles, and the diminished loss of moisture from the skin. Later there is a reduction in the quantity of urine, and the specific gravity rises, but there is no evidence that this is due to retention of water in the tissues. There is an increased loss of water by the lungs, and in many cases by the skin and lungs; the intake of water may also be below the normal, and the thirst of the patient may be unsatisfied. These factors may afford an adequate explanation, but many observers have maintained that the normal proportion of fluid in the body may not persist during fever; the tissues may become drier at one time, and at another water may be retained to fill up the spaces left by the removal of fat and protein. The view that water was retained in some cases of fever was supported by the interesting fact that the urine may become almost or quite free from chlorides. This subject, however, is one of great difficulty, for some observers* have maintained, as the result of careful experiments upon patients, that the retention of chlorides is due entirely to the deficiency in the intake of salt in the food. The tissues contain a relatively large amount of potassium, but only a small amount of sodium, and a certain proportion of sodium chloride appears to be essential for metabolism.

The increased protein disintegration which is present during fever is shown in the urine by the increase in the urea, uric acid, ammonia, sulphates, and phosphates. Such a change, however, is not peculiar to fever, for during inanition in healthy subjects similar changes occur; the same remark applies to the presence of acetone. There is a change in the relative quantity of the different nitrogenous constituents found in the febrile urine. Leathes† found that during pyrexia produced by the injection of the anti-typhoid vaccine there was an increased output of both creatinin and of uric acid, but the increase was most marked in the latter.

The increase in the urinary pigments‡ is absolute, and is not due

* See Garratt, *loc. cit.*, and Sollmann, *Amer. Journ. Physiol.*, 1903, vol. viii., p. 155.

† *Journ. Physiol.*, 1906, vol. xxxv., p. 205.

‡ Garrod, Bradshaw Lecture, *Lancet*, November 10, 1900.

to concentration of the urine. Abnormal pigments are present. Urobilin is found in nearly all febrile disorders, and persists during the period of pyrexia ; whereas in normal urine it is absent as such, and is represented only by small amounts of its chromogen. Hæmatoporphyrin may also be present in febrile urine.

Proteins may occur in the form of either albumins or albumoses, but their significance appears to be different. The albumins are regarded as a sign of a direct toxic effect exerted by the pathogenetic organisms or their products upon the kidneys, as in cases of scarlet fever and diphtheria, whereas the albumoses are probably due to the abnormal destruction of protein in the general tissues of the body.

The behaviour of the sweat-glands during fever is of special interest on account, not only of their relationship to the loss of heat, but also of the differences which are observed during the various stages of fever or in special diseases. As a general rule, sweating is absent during the rigor and fastigium, but is pronounced, or even profuse, during defervescence. In some fevers, however, such as rheumatic fever, septicæmia, and acute miliary tuberculosis, sweating is often marked during the fastigium. These facts show that the activity of the glands is not determined by the temperature or the circulation of the blood in the skin. Moreover, during the crisis of a fever the temperature begins to fall before sweating is observed. It appears that the toxic effect of the disease influences the nervous control of sweating, that the inhibitory effect varies with the disease, and, when present, is neutralized by the development of antibodies. In this way may be explained the outbreak of sweat at the crisis.

The mammary gland in nursing mothers is affected during fever; the secretion is greatly diminished, or may cease.

**The Effect of Fever on Respiration.**—In addition to the remarks which have been made already upon the respiratory exchange during fever, it is necessary to consider the respiratory movements. They are more rapid during pyrexia, even when there is no disease of the lungs or other parts of the respiratory tract. It is impossible, however, to state the extent of the alteration in the pulmonary ventilation, for there are not sufficient data. In some cases the amount of air breathed is, without doubt, much above the normal. The causes of the quick breathing are complex, but they can be arranged in two groups—the quality and quantity of the blood which supplies the respiratory centre in the medulla oblongata, and the nervous impulses from many sources, but especially from the lungs. The influence of the blood depends not only upon the carbon dioxide and oxygen, but also upon its other constituents and upon its temperature. The last factor is one which has been clearly recognized and demonstrated by experiments. A rise in the temperature of healthy men during exposure to heat is accompanied

by an increased rate of breathing, the increase being about three for each degree Fahrenheit (five to six per degree Centigrade).*

The chemical factors are the most important. A rise in the pressure of the carbon dioxide in the blood increases the rate of respiration† in healthy men, but there are not sufficient observations‡ upon this point in cases of fever. In some the percentage of carbon dioxide in the alveolar air of the lungs is below the normal, and it would appear that the acidosis present during fever is another factor in the causation of the rapid respiration. Bound up with the production of acidosis is the question of a deficient supply of oxygen, due either to cardiac failure or to mechanical interference with the free interchange of gases in the lungs.

Nervous impulses affect the rate and depth of respiration, and painful impressions may produce in this way a great effect.§

**The Effect of Fever on the Circulation.**—During fever changes in the circulation are associated with the altered metabolism and rise of temperature. The causes of these changes are as complex as those of the whole process of fever. In the first place there is the influence of the rise of temperature. In a healthy man, whose temperature has been raised by exposure to moist heat, the pulse is quickened about 14 beats per degree Fahrenheit (25 per degree Centigrade)‖; so distinct is this relationship that Liebermeister taught that in fever the rate of the pulse and the temperature followed parallel lines. Under these two conditions there are also similar disturbances in the vasomotor control; a change of posture from reclining to standing will increase the rate of the pulse from 120 to 156 per minute, and produce in the subject a sensation of dizziness. Other factors, however, besides increased temperature come into play. The dilatation of the peripheral bloodvessels lowers the blood-pressure, and the increased rate of the heart-beat may be in part an effort of compensation. This view is supported by the beneficial effects of sponging with cold water. The improvement in the patient's condition is often out of proportion to the reduction in his temperature, and the muscular tone of his body is increased by the action of the cold water upon the sensory nerves and the cutaneous bloodvessels.

Fever is a state of inanition, and this in itself is a cause of cardiac weakness and imperfect compensation in the vascular system. There is also the influence of the toxic action of bacterial products upon the heart and circulation, and this in diphtheria may lead to fatal cardiac failure.

* Haldane, *Journ. Hyg.*, 1905, vol. v., p. 494; Sutton, *Journ. Path. and Bact.*, vol. xiii., 1909, p. 62.

† See p. 433.

‡ Loewy, *Arch. path. Anat. u. Physiol. u. klin. Med.*, Bd. cxxvi., 1891, s. 218; Beddard and Pembrey, *Brit. Med. Journ.*, August 29, 1908.

§ Yandell Henderson, *Amer. Journ. Physiol.*, vol. xv., 1909-10, p. 385.

‖ Sutton, *Journ. Path. and Bact.*, vol. xiii., 1909, p. 62; Haldane, see p. 507.

It is obvious from the foregoing remarks that the condition of the circulation may vary during the different stages of a fever. During the rigor the blood-pressure may rise, for the cutaneous arterioles are constricted and the heart is beating quickly. Later the pressure falls, and the pulse may become very dicrotic, for the tone of the bloodvessels has been diminished and the contractions of the heart are weaker.

**The Effect of Fever on the Nervous System.**—During fever the disturbance in the nervous system is undoubted. Even in the early stages there are signs of a general sensory disorder, headache, and depression; the patient feels unwell, and is disinclined to physical or mental work. There is a lack of nervous control, which is shown in the disturbance of the various systems of the body. At one time this nervous instability produces increased activity, as shown by shivering, restlessness, convulsions, and delirium; at another time depression, as shown by listlessness, unconsciousness, or it may be coma.

The chief cause of these effects appears to be the direct toxic action of the bacterial products, for the nervous symptoms are often antecedent and out of proportion to the rise of temperature. The toxin appears to act as a poisonous drug; the effects may vary with the dose, and opposite results may be produced.

The next important factor is the rise of temperature. Experiments upon healthy men exposed to moist heat show that irritability, restlessness, and failure of mental power and control, are associated closely with the rise in the temperature of the body. In such cases, as also in patients suffering from fever, the application of cold water to the surface of the skin produces a prompt improvement.

Other factors there may be—abnormal products of metabolism, alterations in the quantity and quality of the blood which supplies the brain—but these and the gross changes in the nervous system are considered elsewhere.*

**The Causes and Theory of Fever.**—Before any attempt can be made to discuss these questions, it is necessary to define once more the meaning which is attributed to the term "fever." In different parts of this article it has been insisted that fever is something more than a condition of hyperthermia, notwithstanding the fact that the word has been and is used frequently by both the physician and the layman in the sense of a rise of temperature. Evidence has been given to show that heatstroke produced by exposure to a hot and moist atmosphere is not a condition of pyrexia, but one of hyperthermia; this applies also to the rise of temperature produced by injury to the central nervous system or by the action of drugs.

"Fever" is a convenient term for a group of phenomena with

* See p. 530, also article by Mott.

a more or less definite origin and sequence, and among these phenomena a rise of temperature is generally, but not invariably, found. The process of fever is a complex one, which must be considered in relation to the great questions of infection and immunity, for only when it is viewed in this light is it possible in some degree to understand its different stages. Fever may be defined as *a response in metabolism to the invasion of micro-organisms and a toxic disturbance of the nervous regulation of temperature.* The body is infected by a micro-organism which multiplies and produces poisonous substances or toxins. The early effects are shown upon the nervous system, impulses are discharged down the vaso-constrictor nerves, the cutaneous bloodvessels are contracted, the skin becomes pale and cold, and shivering occurs. The loss of heat is diminished, and in many cases the production is increased; the internal temperature of the body rises above its optimum, and this in turn produces an increased metabolism. The affected nervous system no longer maintains the temperature and metabolism of the body at the normal level. The response of the body to the infection is the production of antibodies or other forms of antagonism, and in the natural course of a fever compensation will occur at a certain stage. In this way the different course run by febrile diseases due to specific micro-organisms may be explained.

Whether such a view be correct or not, the question arises: Is the high temperature beneficial, harmful, or indifferent, in its effect upon the course of the disease and the restoration of the patient to health? Opinions have been divided, have changed from time to time, and have produced a corresponding variation in the treatment of fevers. For centuries* both physician and layman regarded the rise of temperature as a favourable sign in fevers, as evidence of Nature's attempt to destroy and remove the disease-producing material, to purge the body by fire. The rise of an opposite school of thought was due to various causes. The treatment of fevers by cold water so successfully followed by James Currie† in England, and later by Liebermeister‡ in Germany, produced a reaction, which was accentuated by the beneficial effects obtained by the use of an antipyretic, such as quinine, in malarial fever. The experimental method showed that serious or even fatal results could be produced in healthy animals by external conditions of heat which raised the temperature of their bodies. A rise of temperature was regarded as the danger of a fever, and Liebermeister taught that it exerted a deleterious influence on all the organs of the body. New antipyretics were discovered, and became very popular agents in

* See Lorain, *De la Temperature du Corps Humain*, Paris, 1877.

† *Medical Reports on the Effect of Water, Cold and Warm, as a Remedy in Fever and Other Diseases*, Liverpool, 1798.

‡ Volkmann, *Klinischer Vorträge*, No. 31, 1871.

treatment. The meaning of "fever" was confused by the consideration of cases of hyperthermia, such as heatstroke, in which a vicious circle is formed, the rise in the temperature of the body increasing the production of heat. Such a case, it is true, demands the reduction of the temperature of the body, for there is no invasion by a specific micro-organism which must be resisted by the development of antibodies.

In recent years a return to the old view has been brought about by the increasing knowledge of the processes of infection and immunity. Experiments* upon animals show that a high temperature enables them to resist more successfully the effects of pathogenetic organisms, and bacteriological investigations prove that the growth of many bacteria is arrested or their virulence attenuated by a degree of heat such as often obtains in fever.

The beneficial action of quinine is not due to the reduction of temperature, but to its direct action upon the malarial parasite. Moreover, extended experience has shown that many of the antipyretics are useless, or even harmful, in the treatment of fevers. The good effects produced by sponging with cold water a patient suffering from fever are often out of proportion to the reduction in his temperature, and may be due to the improvement in the vascular tone and the nervous system produced reflexly by the cutaneous stimulation. Statistics show that the mortality from fevers does not run parallel with the temperatures observed during the disease. A high temperature, apart from hyperpyrexia, is a favourable sign in prognosis.

**The Limits of Bodily Temperature compatible with Life.**—The range of internal temperature in a healthy man is about 2° (3·6°) under the most varying conditions of work, food, clothing, and climate. A far wider range, however, is observed in certain pathological conditions. Temperatures as low as 24° (75·2°) and as high as 46° (114·8°) have been recorded in patients who have recovered. There are on record cases of higher temperature, but they are not free from sources of error, such as incorrect thermometers, or deception on the part of the patient, such as compression of the thin bulb of a thermometer, friction, or the placing of the bulb in a hot linseed poultice.

Low temperatures may persist for hours, or even days, without a fatal issue, but very high temperatures quickly cause death. The changes which occur in such cases have already been discussed.†

* Loewy and Richter, *Berliner klin. Wochenschr.*, 1897, No. 9.

† See pp. 528 and 530.

## CHAPTER XIII

# THE PATHOLOGY OF DIGESTION

By ARTHUR F. HERTZ

## I. THE SALIVA.

THE chief functions of saliva are mechanical. It prepares the food for swallowing by moistening and softening it and covering it with a layer of mucus. It facilitates taste by dissolving dry substances and bringing them into intimate contact with the taste-buds; it helps to keep the mouth and teeth clean; it dilutes irritant and otherwise injurious substances, and makes it possible to eject them by spitting. Saliva also contains a ferment—ptyalin—which converts soluble starch into dextrin and maltose, and has a similar but less powerful effect on glycogen. This function is not, however, of great importance owing to the amylolytic properties of the pancreatic and intestinal juices.

All food stimulates the flow of saliva rich in mucus and ptyalin; acids produce the most abundant flow, salts and bitter substances rather less, and sugar very little. Caustic substances give rise to an abundant secretion. Mechanical stimulation of the mouth by large objects has no effect, but dry food causes a more abundant secretion than liquid food, and insoluble powders, which require mixing with water before they can be swallowed or spat out, cause a secretion of watery saliva. The flow of saliva is always much increased by thorough mastication.

The secretion of saliva, which occurs when food, chemical substances and insoluble powders are introduced into the mouth, is partly reflex, the afferent impulse being carried chiefly by the glossopharyngeal nerve. But it is partly psychical in origin, as the mere sight, smell or idea of food, or the belief that acid, bitter or dry substances are about to be introduced into the mouth, produces a flow of saliva, which is of precisely the same character as that which is secreted when the substances are actually present in the mouth. Probably the initial secretion is always psychical in origin, the flow being maintained by chemical and mechanical reflexes.

1. **Excessive Secretion of Saliva—Ptyalism.**—Salivation is caused by chemical or reflex stimulation. The former is produced by the

specific stimulating action of certain drugs, such as pilocarpine, and also by drugs, such as the iodides and mercury, which are partially excreted by the salivary glands, the cells of which they irritate.

The flow of saliva can be increased by reflexes originating in the mouth and at a distance. Thus all pathological conditions in the mouth and its neighbourhood, such as stomatitis, cancer of the tongue and carious teeth, especially if associated with pain, are accompanied by salivation. Trigeminal neuralgia, whatever its cause, is frequently associated with a reflex flow of saliva.

Mechanical irritation of the œsophagus causes a secretion of saliva, the afferent impulse being conveyed by the vagus. This is well seen in the salivation, which follows the passage of a tube into the stomach. It also occurs when a large bolus of food or a foreign body becomes lodged in any part of the œsophagus. This does not produce a peristaltic wave, as it would do in the intestine, but merely a local contraction, which does not dislodge the object. But the reflex flow of saliva makes it necessary to swallow, and each act of deglutition helps to propel the foreign body into the stomach. The same reflex is the cause of the salivation, which is a common symptom in cancer of the œsophagus.

When the acidity of the gastric contents is abnormally high, an impulse is conveyed by the vagus to the salivary centre in the medulla, and reflex salivation results. Consequently ptyalism occurs at the height of digestion in many cases of gastric and duodenal ulcer. The excess of alkaline saliva tends to diminish the deleterious effects of the gastric hypersecretion.

The salivation which may occur during menstruation and in the early months of pregnancy is also probably reflex in origin.

Salivation is a common symptom in bulbar paralysis. This is partly a reflex result of the irritation produced by food, which lodges in the pharynx and œsophagus owing to the dysphagia, and is partly perhaps central in origin, the slow degeneration of the cells of the centre resulting in their constant irritation; this would be analogous to the fibrillary twitching of muscles, which may occur in degenerative conditions of the anterior cornu cells of the spinal cord.

Excessive salivation may interfere with digestion by diluting the gastric juice, the secretion of which is also to some extent inhibited by the sodium bicarbonate it contains. Every time saliva is swallowed some air passes with it into the stomach, which may therefore become distended with swallowed air.

2. **Deficient Secretion of Saliva—Xerostomia.**—The dry mouth which is constantly present in fevers, especially typhoid fever, is due mainly to deficiency in the psychical, chemical and mechanical stimuli to salivary secretion. It is probable that the toxins of the diseases also exert some direct inhibitory action on the gland cells. Depressing emotions and loss or perversion of taste, such as occurs

when the tongue is furred, result in a diminution in the psychical secretion. The secretion of saliva is also diminished when excessive quantities of fluid are lost by other channels, as in diabetes and severe diarrhœa. Diseases of the salivary glands themselves, such as mumps, generally result in a diminished secretion. Severe xerostomia occasionally develops without any obvious cause. Lastly, the secretory nerve endings are paralyzed by atropine.

Deficient secretion of saliva causes the mouth to become septic, as particles of food remain between the teeth, where they undergo bacterial decomposition. The food is insufficiently chewed and is therefore likely to irritate the stomach.

3. **Qualitative Abnormalities of Saliva.**—Saliva has been supposed to become acid in reaction under certain conditions, but, with the possible exception of rare cases of severe diabetes, it is always alkaline when secreted, the acidity of the fluids in the mouth being due to the formation of lactic acid by bacterial activity.

The amylolytic action of saliva is said to be diminished in advanced tuberculosis, severe heart failure and prolonged fevers.

Urea may be present in the saliva in Bright's disease, but sugar and bile are never secreted by the salivary glands.

## II. DEGLUTITION AND THE ŒSOPHAGUS.

As soon as the food has been sufficiently masticated, it is carried by a voluntary effort to the back of the tongue, a sudden jerk of which shoots it into the mouth of the œsophagus. The latter is closed in the resting condition, but is opened in the act of swallowing, as a result of the larynx being drawn upwards and forwards until its vestibule is covered by the base of the epiglottis. The mouth and naso-pharynx are simultaneously shut off from the pharynx, which thus becomes a closed cavity. The contraction of the muscles surrounding it produces a considerable rise in pressure, which plays an important part in the passage of the food down the œsophagus, because the slight negative pressure of the thorax prevails in its lower two-thirds. The rise in intrapharyngeal pressure is not, however, sufficient to propel the food into the stomach, the wave of contraction which passes down the œsophagus being of greater importance, particularly when solid food is swallowed.

Food passes rapidly down the œsophagus as far as the cardia, through which it runs into the stomach at a comparatively slow rate, as in spite of the relaxation of the cardiac sphincter, which occurs when the wave of contraction reaches the end of the œsophagus, the orifice remains sufficiently small to offer a distinct obstacle to the onward passage of the food. The time which elapses between the commencement of deglutition and the disappearance of the last trace of food from the œsophagus is about

five seconds, about one-half of the period being spent in the passage through the pharynx and œsophagus and the other half in the passage through the cardia. The delay in the last part of the œsophagus is of practical importance when strong acids or alkalies are swallowed: the upper part of the œsophagus frequently escapes serious injury, but the lowest inch or two are badly damaged, owing to the irritant being longer in contact with them.

The swallowing reflex is initiated by the contact of food with the mucous membrane of the pharynx. The impulse is conveyed by the superior laryngeal nerve to the bulbar centre, which is in close connection with the vagus nucleus; the efferent impulses pass down branches of the vagi to the pharynx, the recurrent laryngeal nerves to the upper third of the œsophagus, and the vagi to the lower two-thirds and the cardiac sphincter. Complete transverse division or excision of a segment of the œsophagus does not interfere with the regular transmission of the wave of contraction, which depends mainly upon a series of nervous impulses reaching successive segments. The muscular coat of the upper third of the œsophagus is composed of striated fibres, and that of the lower two-thirds of unstriated fibres.

When the soft palate is paralyzed, as in diphtheritic neuritis, the naso-pharynx cannot be shut off from the rest of the pharynx during the act of deglutition. Part of the food is consequently propelled into it instead of into the œsophagus, and fluids may escape through the nostrils. At the same time the normal rise of pressure in the pharynx cannot occur, and dysphagia results. In bulbar paralysis, the tongue, palate and pharyngeal muscles are paralyzed, and swallowing becomes impossible. When the vagi are injured below the origin of the recurrent laryngeal nerves, swallowing is only temporarily impaired, as the unstriated fibres are still capable of automatic activity so long as their peripheral nerve centres are intact. If, however, the nerve to the upper third of the œsophagus is simultaneously destroyed, swallowing becomes permanently impossible, as the striated muscle fibres of the upper third of the œsophagus lose their tone and contractibility. Disease of one recurrent laryngeal nerve, however, does not interfere with swallowing; consequently dysphagia only results from bilateral nervous lesions, such as symmetrical disease of the bulbar nuclei or of the peripheral nerve fibres of both superior laryngeal or both recurrent laryngeal nerves. When the irritability of the medulla is greatly depressed, as in deep coma, a similar dysphagia results. In such cases it is possible to introduce food into the stomach, if a tube be passed into the upper thoracic region of the œsophagus, as the paralyzed striated muscle fibres are there replaced by the still active unstriated fibres.

**The Cardiac Sphincter.**—Stimulation of the vagi causes relaxation of the normal tone of the cardiac sphincter. The series of impulses

arising in the swallowing centre during deglutition, which cause successive segments of the œsophagus to contract, ends by causing the cardia to relax. Absence of this relaxation is probably the cause of the rare condition commonly known as *idiopathic* or *primary dilatation and hypertrophy of the œsophagus*, in which the whole or the lower part of the œsophagus is enormously dilated and its muscular coat greatly hypertrophied, although no mechanical obstruction is found after death. Absence of relaxation of the cardia causes food to collect in the œsophagus, which consequently dilates; hypertrophy then occurs, owing to the repeated attempts of the œsophageal musculature to overcome the resistance at the cardia. This condition has been ascribed to "cardiospasm," but as no hypertrophy of the cardiac sphincter is found after death the theory is untenable.

The tone of the cardiac sphincter depends to a great extent upon the acidity of the gastric contents. Regurgitation into the œsophagus requires a much greater rise in intragastric pressure when there is excess of free acid in the stomach than when the quantity is normal, and in the latter case than when it is deficient. The acid controls the tone of the cardia by a local reflex, which originates in the mucous membrane in the immediate neighbourhood and is quite independent of the vagi and splanchnic nerves. Reflex relaxation of the cardia also occurs when the intragastric pressure reaches 20 millimetres of mercury.

**Œsophageal Obstruction.**—In addition to the dysphagia, which results from interference with the nervous control of swallowing, swallowing may be rendered difficult or impossible by functional and organic obstruction of the lumen of the œsophagus. Spasmodic contraction of a small segment of the œsophagus occurs not infrequently in neurotic individuals, but it never gives rise to serious dysphagia. It is due to excessive irritability of the nerve centres which control the organic functions of the body. Spasm may also occur as a result of local irritation, as when a foreign body becomes impacted or when the mucous membrane is ulcerated.

FIG. 124.—TRACING, AFTER BISMUTH MEAL, OF A DILATED ŒSOPHAGUS, THE RESULT OF CANCER OF THE CARDIA.

Organic obstruction is produced by cicatrization following the injury inflicted by caustic poisons, and by epithelioma. In both cases the proximal part of the œsophagus attempts to overcome the resistance offered to the passage of food by increased peristalsis, which in time results in hypertrophy of the muscular coat. If the obstruction is progressive, a time comes when the increased peristalsis is only able to force food through the narrow passage with

extreme slowness, with the result that it accumulates above the obstruction (Fig. 24). No great degree of dilatation occurs in the œsophagus above the obstruction, as the food does not long remain in it, but regurgitates into the mouth as a result of antiperistalsis without the aid of the diaphragm and abdominal muscles, which contract in ordinary vomiting.

## III. THE MOTOR FUNCTIONS OF THE STOMACH.

### A. Tone.

The tone of the stomach adapts itself to the volume of its contents in such a way that the minimal intragastric pressure remains steadily between 4 and 6 millimetres of mercury whether the organ is full or almost empty. Consequently the position of the upper limit of the semifluid gastric contents varies very little so long as more than 40 c.c. are present, and the greater curvature is only slightly depressed as the stomach is gradually filled (Fig. 25). No peristalsis occurs in the proximal half of the stomach, which acts as a storehouse for the food. A gradual increase in the tone of its muscular coat causes its capacity to be slowly reduced, with the result that its contents pass into the active pyloric half, where they replace the chyme as it is discharged into the duodenum.

1. **Deficient Tone—Atony, Hypotonus.**—Deficient tone may be due to (*a*) changes in the muscular coat itself and to (*b*) changes in the nervous mechanism which controls the tone.

(*a*) *Changes in the Muscular Coat.*—The disturbances in gastric digestion, which are caused by the malnutrition resulting from the consumption of insufficient food, anæmia, tuberculosis and cancer, and by the toxæmia of acute fevers, are due in part to atony of the muscular coat of the stomach. But no actual atrophy or degeneration has been found after death in these conditions, comparable to that which is so evident in the skeletal muscles. The absence of gross anatomical changes does not, however, preclude the possibility of functional disturbances, which are either entirely independent of structural alterations or are due to changes too fine for recognition by the ordinary methods of investigation. Such functional disturbances would be analogous to those occurring in the heart, in which dilatation due to deficient tone is a frequent symptom of chlorosis and acute fevers without being accompanied by any corresponding structural changes. Possibly the feeble digestion in extreme old age is due to a similar loss of tone.

Chronic catarrh of the gastric mucous membrane resulting from chronic irritation may lead to atony of the muscular coat, which is sometimes associated with definite degenerative changes recognizable on microscopical examination.

Habitual overeating and overdrinking lead to atony, especially

if the stomach is filled rapidly. The gradual filling of the stomach when a very large meal is slowly eaten is much less harmful; moreover the total distension is less, as a larger proportion of the contents leaves the stomach whilst the meal is being eaten. Under normal conditions the muscle fibres relax as the stomach becomes filled, and the bundles of muscle fibres undergo a rearrangement, which results in an increase in its capacity. But when the stomach contains more than a certain quantity of food, the muscle fibres become stretched as well as relaxed, and the bundles of muscle fibres are forcibly separated from each other. If the overdistension is excessive on even a single occasion, the elasticity of the muscle fibres and of the connective tissue may be insufficient to restore the stomach to its normal size when the gastric contents have been evacuated. More often it is only after the stomach has been repeatedly stretched as a result of habitual overeating that a permanent loss of tone results.

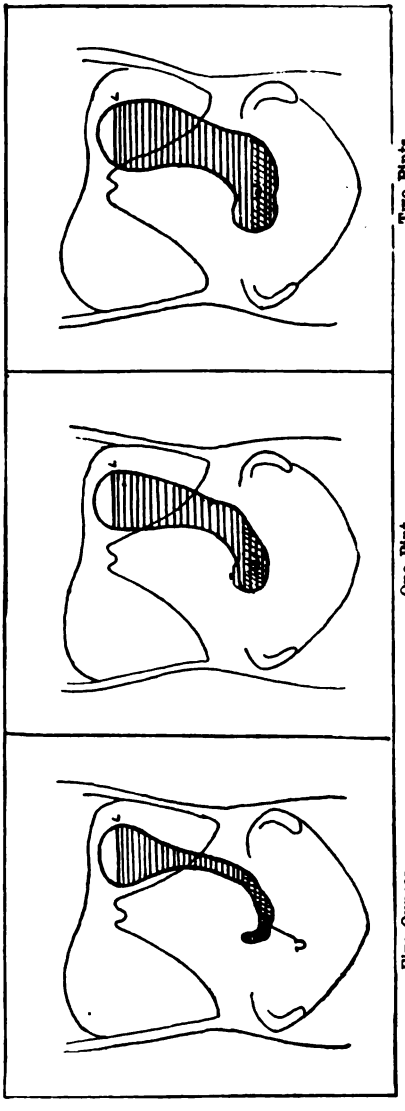



FIG. 25.—TRACINGS OF STOMACH AT DIFFERENT STAGES DURING THE CONSUMPTION OF A BISMUTH MEAL. *L*, Horizontal upper limit of gastric contents; *U*, umbilicus.

When the passage into the duodenum is delayed as a result of pyloric obstruction, the stomach contains a large quantity of food for many hours in the day and may never be completely empty. Under normal conditions food is constantly leaving the stomach whilst a meal is being eaten; but when there is well-marked pyloric obstruction, almost all the food and almost all the gastric juice recreted are still present at the end of a meal, so that the stomach

is abnormally distended. The prolonged distension results in atony, the degree of which depends upon the degree of obstruction and the rate of its development. If it develops slowly, the muscular coat of the pyloric end of the stomach hypertrophies ; consequently but little delay in evacuation and no atony occur at first. At a later stage, when the hypertrophy is insufficient to compensate for the obstruction at the pylorus, stagnation and atony occur. When the obstruction is rapidly progressive, as in most cases of pyloric cancer, there is less hypertrophy, and atony begins to develop at a very early period.

(*b*) *Changes in the Nervous Control of Gastric Tone.*—Conditions, such as neurasthenia, which lead to depression of the central nervous system tend to cause a diminution in the excitability of the peripheral nervous mechanism, upon which the tone of the stomach depends.

**Results of Gastric Atony.**—When atony is present, the stomach is no longer able to adapt itself accurately to the volume of its contents. The intragastric pressure is therefore reduced, and the upper border of the gastric contents no longer remains constant whatever quantity of food is present. Food taken when the stomach is empty drops at once to its most dependent part, instead of being held up for a few moments by the tonic contraction of the body of the stomach. As more and more food is taken the upper limit of the gastric contents gradually rises, but it never reaches the height which is reached under normal conditions with as little as 40 c.c. At the same time the gastric tone is insufficient to withstand the weight of the food, so that the lower border of the stomach sinks as the quantity of gastric contents increases (Fig. 26). The final increase of tone, which normally causes the lower border of the stomach to rise above its original level just before the stomach becomes completely empty, does not occur. The condition produced is known as *atonic dilatation of the stomach.* Peristalsis frequently remains normal in spite of the presence of a considerable degree of atony. Except in extreme cases, the gastric contents begin to pass into the duodenum immediately after their entry into the stomach, and the evacuation continues at the normal rate. Only the last traces of the food remain abnormally long in the stomach. This is due to the tone not increasing sufficiently to enable the contents of the most dependent part of the body of the stomach to pass into the pyloric end. In cases of extreme dilatation due to severe chronic obstruction of the pylorus, the size of the stomach is so great that the upper surface of the food does not reach the lesser curvature in the vertical position, and consequently none of the food reaches the pylorus or passes into the duodenum until the horizontal position is assumed.

2. **Excessive Tone—Hypertonus.**—Hypertonus may result from (*a*) absence of distension and from (*b*) certain reflexes.

(*a*) *Absence of Distension.*—When food is taken in small quantities at frequent intervals, the stomach is never distended, and its tone gradually increases. This is particularly well seen in patients who have been strictly dieted for some weeks, especially if they have been kept in bed. Owing to the abnormally rapid evacuation of the stomach in achylia gastrica, this condition is also associated with hypertonus.

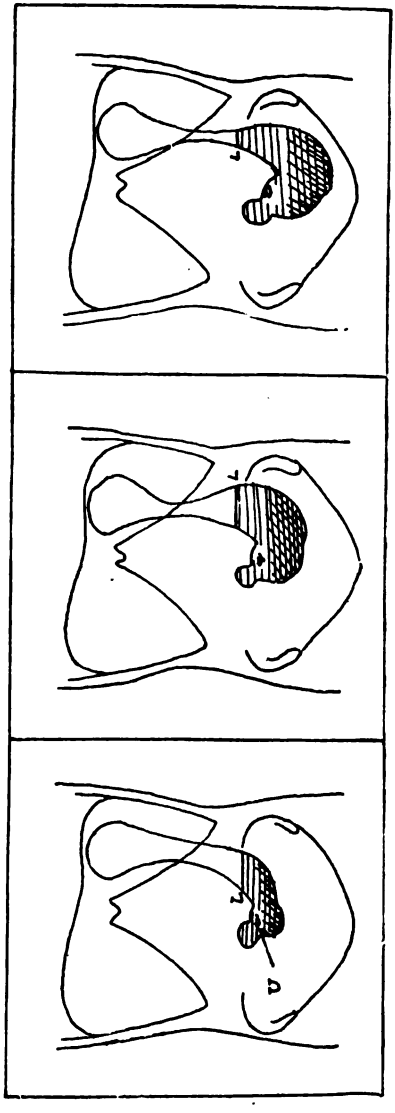


FIG. 26.—TRACINGS OF AN ATONIC STOMACH AT STAGES CORRESPONDING TO THOSE OF FIG. 25.

(*b*) *Reflex Hypertonus.*—The most common cause of hypertonus is duodenal ulcer. The increased tone is probably due to a reflex produced by irritation of the surface of the ulcer by the acid chyme. Reflex hypertonus also occurs, but much less constantly, with gall-stones and chronic appendicitis. In most cases reflex hypertonus is accompanied by reflex hypersecretion. Hypertonus and hypersecretion may also occur together in the absence of organic disease, but the association either predisposes to ulcer or is actually the result of some not clearly recognized pre-ulcerative condition of the duodenum.

**Results of Gastric Hypertonus.**—A comparatively small quantity of food is sufficient to produce a rise in intragastric pressure. The greater curvature of the stomach is abnormally high, and even after a large meal its lowest point may be one or more inches above the umbilicus in the vertical position (Fig. 27). As the activity of peristalsis is often simultaneously increased, the food passes with abnormal rapidity into the duodenum.

## B. Spasm.

1. **Localized Spasm.**—Spasm of a narrow band of circular muscle fibres occurs not infrequently in gastric ulcer; more rarely it may be observed in the absence of any organic lesion. It leads to a tem-

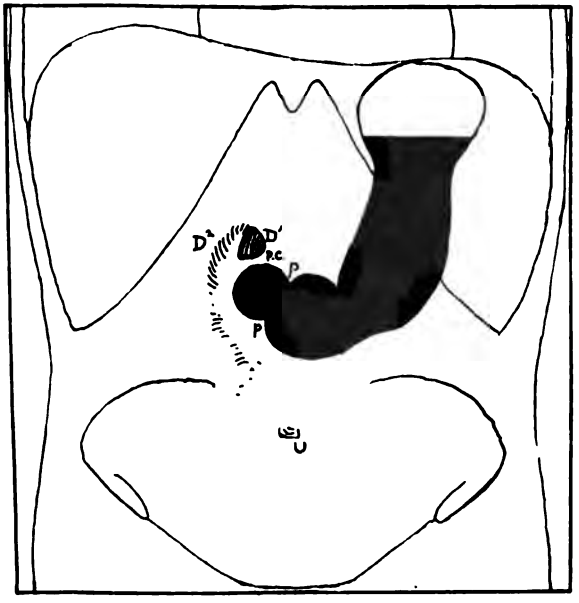



FIG. 27.—HYPERTONIC STOMACH OF DUODENAL ULCER.
*U*, Umbilicus; *PP*, peristaltic wave passing towards the pylorus; *P.C.*, pyloric canal; $D^1$, first part of the duodenum; $D^2$, second part of the duodenum.

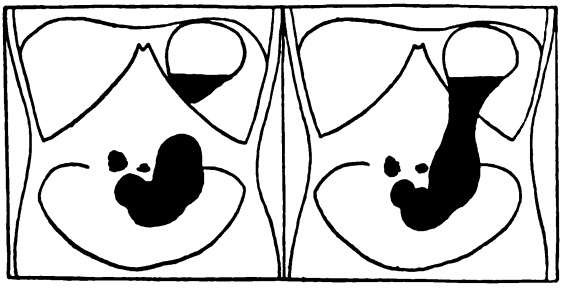


FIG. 28.—TRACINGS OF STOMACH, SHOWING SPASM DUE TO A GASTRIC ULCER, AND ITS DISAPPEARANCE AFTER MASSAGE.

porary condition of hour-glass stomach, the ulcer being generally situated at the corresponding point on the lesser curvature. The spasm is most marked whilst a meal is being eaten; it may last

for a few minutes or several hours at a time. It is never sufficiently strong to cause any considerable degree of obstruction, and consequently neither well-marked stasis nor increased peristalsis occurs in the proximal segment (Fig. 28).

2. **General Spasm (Stiffening).**—A spasmodic increase in tone of the whole stomach sometimes occurs as a result of organic obstruction of the pylorus. Pyloric obstruction generally leads to increased peristalsis only, but occasionally the whole of the stomach becomes suddenly "stiff," owing to a great and general increase in its tone, which lasts only for a few seconds.

### C. Peristalsis.

Peristalsis begins as soon as food enters the stomach. Each wave starts as a contraction near the middle of the greater curvature, and it deepens as it slowly progresses towards the pylorus. About one inch from the entrance to the pyloric canal it reaches such a depth that part of the pyloric vestibule becomes almost completely separated from the rest of the stomach, and in some cases the separation is finally complete. The part thus cut off then diminishes still further in size owing to the progress of the peristaltic wave. As a result, some of its contents are from the first forced through the pyloric canal, the remainder passing back as an axial reflux stream into the stomach. The peristalsis breaks up the food and mixes it thoroughly with the gastric juice. The contents of the pyloric half of the stomach are consequently more fluid and more homogeneous than those of the cardiac half. The waves occur at regular intervals of fifteen to twenty seconds, and three or four are present simultaneously. They increase in strength as digestion proceeds, and continue without intermission until the stomach is empty between one and four hours after the meal, the exact time depending on the bulk and composition of the food.

The mechanical stimulants of peristalsis are more important than the chemical, for its activity does not vary greatly according to the nature of the food so long as the bulk and consistence are unaltered. The stretching of the muscular coat by the food as it enters the stomach is the chief stimulus to peristalsis. The mere contact of smooth objects with the gastric mucous membrane has no effect, but irregularly-shaped objects, especially if they are hard, stimulate it. The activity of peristalsis thus varies with the consistence of the food which reaches the stomach; this depends partly on the quantity of cellulose and other indigestible material present in it, partly on the amount of softening which has taken place in cooking, and partly on the extent to which further subdivision and softening have resulted from chewing.

The chief chemical stimulants of gastric peristalsis are hydrochloric acid and the extractives of meat. Alcohol also stimulates

peristalsis, and carbohydrates and proteins produce more active peristalsis than an equal quantity of fat of the same consistence.

When a peristaltic contraction begins near the centre of the stomach, it produces a shallow depression, which is not infrequently visible post mortem. This is not, however, fixed, but moves along as a wave, and it produces nothing approaching a complete division of the stomach into two parts until it reaches the pyloric vestibule. Even then the division, though it is almost complete, steadily moves towards the pylorus and is absent in the intervals between the arrival of the peristaltic waves. The food taken at the beginning of a meal reaches the pyloric end first, and that taken last is at first uppermost. Pepsin is secreted in all parts of the stomach, hydrochloric acid mainly in the cardiac half. Some hydrochloric acid is carried with the first portion of the meal to the pyloric part of the stomach, in which the food and gastric juice are constantly mixed by peristalsis. In the cardiac end there is no peristalsis, so that the peripheral part of the food is most acid, and the central part may remain for a time alkaline and undergo salivary digestion. But there is no sharp division between the composition and reaction of the chyme in the different parts of the stomach, as diffusion of the saliva and soluble constituents of the food on the one hand, and of the gastric juice and products of gastric digestion on the other, constantly and rapidly takes place throughout the stomach, and the movements of the diaphragm, abdominal muscles and body as a whole all help to mix together the contents of the different parts of the stomach.

1. **Deficient Peristalsis.**—The same causes which lead to a loss of tone of the gastric musculature may also cause deficient peristalsis, although tone is more readily affected than peristalsis. Chronic gastric catarrh, especially when it has led to atrophy of the mucous membrane, results in a diminution of its sensibility to the stimuli which normally give rise reflexly to peristalsis. Long-continued irritation of the mucous membrane, apart from the catarrh which it causes, also finally impairs its sensibility. When the nervous system is depressed, stimulation of the gastric mucous membrane produces less powerful peristalsis than normally.

The indigestion which follows depressing emotions is largely due to the inhibition of peristalsis. Inhibition also results from painful diseases and injuries of any part of the body, but particularly of the abdominal viscera. The peritoneum is most active in this connection, mere exposure to air being sufficient to inhibit peristalsis. The nearer the seat of irritation is to the stomach, the greater is the inhibition. Complete cessation of gastric peristalsis occurs immediately if an ulcer of the stomach or duodenum perforates, but not until some time after perforation of the appendix.

When peristalsis is weak, the contractions are not sufficiently

deep to separate the pyloric end of the stomach from the rest of the organ. Consequently the pressure on the gastric contents in the extreme pyloric end of the stomach is not much greater than that in the fundus. As the intragastric pressure is the same as the general intra-abdominal pressure, it is no greater than the pressure in the duodenum. Consequently it is no longer possible for food to be pressed through the pyloric canal into the duodenum, as it is under normal conditions. Food therefore only leaves the stomach when the pyloric sphincter is fully relaxed, and even then the evacuation is much less rapid than under normal conditions. Hence deficient peristalsis gives rise to stasis. It is, however, very rare for peristalsis to be so deficient that the stasis is as great as that which occurs in cases of pyloric obstruction. It may therefore be confidently assumed that pyloric obstruction is present, if any food is found in the stomach twelve hours after a large meal.

2. **Increased Peristalsis.**—Peristalsis is increased by (*a*) excessive stimulation, and (*b*) when excessive force is required to evacuate the contents of the stomach.

(*a*) *Excessive Stimulation.*—The presence in the stomach of excessive quantities of foodstuffs, which stimulate peristalsis as a result of their chemical or mechanical properties, gives rise to abnormally active peristalsis. The only important chemical stimulant in this connection is hydrochloric acid, gastric hypersecretion being generally associated with very active peristalsis, although for other reasons food generally leaves the stomach more rapidly when the hydrochloric acid is deficient than when it is excessive. Most substances which irritate the mucous membrane chemically give rise to vomiting rather than to increased peristalsis when present in excess.

Insufficiently masticated food increases peristalsis, with the result that the muscles of the pyloric part of the stomach do the work which should have been performed by those of the jaws. The mechanical irritation of the mucous membrane thus produced is in all probability an important factor in the pathogenesis of the chronic gastritis so often associated with insufficient mastication, whether this is the result of habit or deficient teeth. The production of ulcer and of cancer of the stomach, both of which occur with far greater frequency in the region of the stomach where peristalsis is active than in the fundus, is probably often in part due to the same cause.

In achylia gastrica the connective tissue of meat is insufficiently dissolved, so that undigested lumps remain for a longer period than usual in the stomach. These stimulate peristalsis and so compensate for the absence of the stimulating action of hydrochloric acid.

(*b*) *Difficult Evacuation.*—Excessive force is required to empty the stomach when hard or bulky objects have to pass into the duodenum, and when the passage into the duodenum is obstructed. Even when

completely relaxed, the pyloric canal is only a narrow passage; but if food is properly cooked and properly chewed, it can be completely evacuated without stretching the canal. On the other hand, when anything which is completely indigestible, such as a coin or other foreign body, or is incompletely digested, such as large insufficiently masticated masses of hard food, is present in the stomach, peristalsis must be unusually powerful in order to force it through the pyloric canal. This powerful peristalsis only occurs after all the softer and more finely divided contents of the stomach have passed into the duodenum. It is so powerful that objects of considerable size, such as pennies, can be forced through the narrow pyloric canal.

Whenever the lumen of the pyloric canal is diminished, excessive peristalsis, which can often be felt through the abdominal wall, is required in order to force the gastric contents into the duodenum. The increased work done by the muscular coat of the stomach under these conditions leads to its hypertrophy. The hypertrophy is confined to the pyloric half of the stomach, and is most marked in the extreme pyloric end. This is due to the fact that the increased work is done chiefly by the pyloric half, and especially by the pyloric vestibule, which becomes completely separated from the rest of the organ by the advancing peristaltic wave. By means of the X rays it has been found, however, that in cases of well-marked obstruction peristalsis begins in the fundus, and not, as under normal conditions, in the centre of the body of the stomach. In rare instances the forward peristalsis is interrupted by occasional waves passing in the reverse direction; this never occurs in the absence of organic obstruction.

Pyloric obstruction is most frequently a result of the cicatrization of a gastric or duodenal ulcer or of cancer. Neither the ulcer nor the cancer originates in the pyloric canal, which may, however, be finally invaded by it. The cicatrization not only results in a diminution in the lumen of the pyloric canal, but it also makes it impossible to stretch it, owing to the small degree of elasticity possessed by scar tissue.

Gastroptosis, which is generally a part only of a general visceroptosis, cannot by itself lead to pyloric obstruction, as any kink which it might produce would be in the duodenum at the point where it becomes fixed, the pylorus being sufficiently mobile to drop with the rest of the stomach when the erect position is assumed. Such a kink in the duodenum only causes obstruction in exceptional cases, any dilatation in a dropped stomach being generally due to co-existing atony.

**The Pylorus and the Evacuation of the Stomach.**—During life the pyloric canal is always closed by the tonic contraction of the sphincter, variations in which regulate the passage of the gastric contents into the duodenum, and even when relaxed for the passage of food the canal is very narrow. Peristalsis is therefore

required, not only for mixing the food with the gastric juice, but also for pressing even finely-divided particles through the pylorus; in the case of larger particles very strong peristalsis is required to overcome the resistance. Peristalsis, however strong, could not press the gastric contents through the pylorus unless the contraction was sufficiently deep to shut off the extreme pyloric end of the stomach completely from the rest, as it would otherwise simply produce a slight rise in the general intragastric pressure, which would be no greater at one end of the stomach than the other. But as the peristaltic wave, when it approaches the pylorus, forms a complete division across the stomach, the further passage of the wave produces a very considerable pressure in this part of the stomach, which is sufficient to overcome the resistance offered by the pyloric canal.

The pyloric sphincter is relaxed when the stomach is empty, and is uninfluenced by the presence of water, which consequently passes rapidly into the duodenum when it is drunk alone. Other fluids, such as milk, bouillon and beer, and water taken with food, leave the stomach much more slowly. It appears, therefore, that the pyloric tone is increased by the entry into the stomach of anything which has the power of stimulating the secretion of gastric juice.

A neuro-muscular mechanism exists at the pylorus, which causes the tonic contraction of the sphincter to diminish on the arrival of each peristaltic wave at the pylorus. The relaxation does not become well marked until free hydrochloric acid appears in the pyloric part of the stomach. Consequently a carbohydrate meal leaves the stomach more quickly than a protein meal, as the former does not combine with hydrochloric acid, whereas proteins combine with the first portion secreted, with the result that a longer period elapses before free acid is present. Fats inhibit the secretion of gastric juice, and consequently their presence in a meal delays the relaxation of the pylorus.

The relaxation of the pyloric sphincter on the arrival of a peristaltic wave is inhibited by certain reflexes, the most important of which results from the presence of free hydrochloric acid in the duodenum. Owing to this reflex no more chyme enters the duodenum until that which arrived immediately before is neutralized by the pancreatic juice and bile, the secretion of which is called forth by the presence of acid in the duodenum. This mechanism keeps the reaction of the small intestine below the opening of the common bile-duct neutral or alkaline, and so allows digestion by the pancreatic ferments to proceed, and at the same time it protects the mucous membrane from the liability to ulceration, which the stomach and the first part of the duodenum owe to the acid reaction of their contents.

Inhibition of pyloric relaxation also occurs when the mucous membrane of the pyloric part of the stomach comes into contact

with anything which might injure the duodenal mucous membrane owing to its mechanical or chemical properties. Hence insufficiently chewed masses of food remain in the stomach until all the fluid and semifluid contents have left, so that more time is given to the gastric juice to soften them and to the gastric peristalsis to break them up. A similar mechanism exists for the protection of the duodenum from injury by exposure to a temperature much above or below that of the body, very hot and very cold food leaving the stomach less rapidly than food at the body temperature. Distilled water and anisotonic saline and sugar solutions also remain longer in the stomach than isotonic solutions, in order that diffusion, osmosis and secretion may render the chyme more nearly isotonic with the tissue fluids by the time that it reaches the duodenum. Thorough mastication divides the food into fine particles, dilutes it and brings it to the body temperature. Under ideal conditions, therefore, the food is so altered in the mouth that little remains to be done in the stomach in order to prepare it for transmission into the duodenum.

**Functional Disturbances of the Pyloric Sphincter.**—Owing to the absence of hydrochloric acid from the stomach in achylia gastrica, the sphincter is permanently relaxed. Consequently the stomach empties itself with abnormal rapidity, although the stimulating influence of hydrochloric acid on peristalsis is absent.

It is generally stated that spasm of the pyloric sphincter may result reflexly from gastric and duodenal ulcer, gall-stones, appendicitis, and even gastric hypersecretion apart from organic disease. But such a spasm would cause obstruction and dilatation, neither of which is found in these conditions unless some complication is present. The tumour, which can sometimes be felt in such cases and which can be seen and felt at operation, is due to the hypertonus of the pyloric vestibule, and is not really a spasm of the pyloric sphincter at all, as the term "pylorospasm," which has been incorrectly applied to it, would suggest. The only condition which can give rise to a true spasm of the pyloric sphincter is an ulcer in the pyloric canal itself. Ulcers rarely, if ever, originate in this situation, but occasionally a gastric or duodenal ulcer may spread until it reaches the pyloric canal. The presence of an ulcer in the canal would in all probability result in spasm whenever chyme passed through it, just as an anal ulcer causes spasm of the sphincter ani during defæcation. In such cases dilatation of the stomach and delay in evacuation may occur, but it is always difficult to exclude organic obstruction due to the swollen tissues which surround an active ulcer.

Inhibition of the relaxation of the pyloric sphincter, which should occur on the arrival of each peristaltic wave at the pylorus, may be associated with the inhibition of peristalsis which results from depressing emotions and painful stimulation of sensory nerves.

This is probably the cause of the delay in the complete evacuation of the stomach, which is occasionally observed in the conditions already mentioned as having been supposed to give rise to pylorospasm. It also occurs independently of inhibition of peristalsis for some hours after an injury has been inflicted upon the upper part of the small intestine. By this means the intestine is protected from irritation by food until sufficient time has elapsed for a certain amount of repair to take place.

### D. Vomiting.

The act of vomiting is preceded by a deep inspiration, at the end of which the glottis is closed, so that the negative pressure in the thorax is increased. Immediately afterwards the abdominal muscles contract strongly. As the diaphragm is held in the position of extreme inspiration, the volume of the abdominal cavity is greatly reduced, and the intra-abdominal pressure is correspondingly increased. As soon as the intragastric pressure reaches 20 millimetres of mercury, a reflex is called forth, which causes the cardiac sphincter to relax. The whole of the pyloric end of the stomach contracts and the fundus relaxes, so that the gastric contents are forced into the latter, from which they are expelled through the relaxed cardia owing to the high intra-abdominal and low intrathoracic pressure. As they pass from the œsophagus through the pharynx and mouth, the soft palate is raised and the posterior pillars of the fauces are approximated in order to shut off the passage through the nose.

The efferent impulses which result in vomiting are carried by the phrenic nerves to the diaphragm, by various other spinal nerves to the abdominal muscles, and by the vagi to the stomach. The co-ordinated activity of these muscles depends upon a centre, which is closely associated with the nucleus of the vagus. It is set in action by (1) impulses coming from higher parts of the brain (central vomiting); (2) afferent impulses from various parts of the body (reflex vomiting); and (3) the direct action of poisons on the nerve centres (toxic vomiting).

1. **Central Vomiting.**—Vomiting is only rarely under the control of the will. But hysterical individuals, after they have vomited a number of times owing to some central, reflex or toxic cause, may suggest to themselves that certain circumstances will invariably cause them to vomit. This is the mode of origin of hysterical vomiting, which can, moreover, be overcome by a counter-suggestion and by persuasion.

Various emotions may result in vomiting, especially in individuals with an abnormally excitable nervous system.

Certain organic nervous diseases, such as cerebral tumour and meningitis, are frequently accompanied by vomiting. This is

partly due to increased intracranial pressure, and partly to direct irritation of higher parts of the brain, from which impulses pass to the vomiting centre.

2. **Reflex Vomiting.**—Reflex stimulation of the vomiting centre is the most common cause of vomiting. The most important source is the stomach itself, the afferent impulses being carried by the afferent fibres of the vagi. Irritation of the mucous membrane by abnormal constituents of the gastric contents, whether introduced in the food or resulting from bacterial decomposition, frequently causes vomiting. This is especially likely to occur if the mucous membrane is inflamed, as in gastritis, or if an ulcer or a growth is present. Overdistension with food, especially if it occurs rapidly, as when a big meal is bolted, or if it is prolonged, as in pyloric obstruction, has the same effect.

Painful stimulation of any afferent nerves, but particularly of those passing from abdominal viscera, such as occurs in the attacks of pain associated with disease of the stomach, in biliary colic, in appendicitis, and in intestinal obstruction and peritonitis, may cause vomiting. Tickling the fauces is a common method of inducing vomiting, the afferent impulse being carried in this case mainly by the glosso-pharyngeal nerve. Vomiting may also be excited reflexly from the lungs in phthisis and from the heart when dilated, and the vomiting of migraine is probably in most cases a reflex from the eyes, owing to errors of refraction, or from the alimentary canal.

Sea-sickness is probably due to a reflex, arising from abnormal stimulation of the semicircular canals and carried by the vestibular nerves. The vomiting in diseases of the ear in which the semicircular canals are directly or indirectly involved, as in Menière's disease, is of similar origin. The vomiting of early pregnancy is probably reflex; when persistent it may be partly toxic in origin, and in hysterical women it is aggravated by auto-suggestion.

3. **Toxic Vomiting.**—Some emetics, such as apomorphine, cause vomiting by direct irritation of the vomiting centre. Others, such as mustard and copper sulphate, act reflexly from the stomach, and are consequently only active when they are swallowed, whilst drugs such as tartar emetic and ipecacuanha act in both ways.

Poisons produced in the body, as in uræmia and in Addison's disease, may irritate the vomiting centre. In uræmia, however, the action is partly reflex, owing to the excretion into the stomach of toxins which should be excreted by the kidneys. The bacterial toxins produced in acute fevers, especially at the onset, often excite vomiting.

## IV. THE SECRETORY FUNCTIONS OF THE STOMACH.

### A. Gastric Juice.

Gastric juice converts the proteins of the food into peptones; it converts caseinogen into casein, which is subsequently digested like other proteins; it has a slight lipolytic action on emulsified fats; it has no action on starch, but it inverts cane-sugar into dextrose and levulose; it softens and dissolves connective tissue; and it exerts an antiseptic action, destroying some and inhibiting the development of others of the numerous organisms which reach the stomach.

The most important stimulus to the secretion of gastric juice is psychical in origin. The idea of food, and still more the sight, smell and taste of food, particularly if it be of an appetizing nature and if the individual be hungry, give rise after a latent period of about five minutes to the secretion of a considerable quantity of very active gastric juice. So long as the food continues to be enjoyed and the appetite remains, this "appetite" or "psychical" secretion continues. It is at once stopped by anger, and does not occur at all when food is eaten without appetite or under depressing conditions. The secretory nerve fibres which convey the stimulus to the gastric mucous membrane are contained in the vagi.

Mechanical and thermal stimulation of the gastric mucous membrane produces no secretion, so that the only secretion of gastric juice, apart from that produced by psychical influences, is due to the chemical properties of the food. Starch and native proteins give rise to no secretion, but the products of starch and protein digestion stimulate the flow of gastric juice. Some unknown constituents of meat juice have the same effect, and water also acts as a feeble stimulant. It was at first believed that the chemical stimulants acted reflexly, but this is not really the case, as the secretion is unaffected by section of all the nerves to the stomach. The injection of an extract of the boiled mucous membrane of the pyloric end of the stomach, made with dextrin, maltose, dextrose, peptone or water, stimulates all parts of the gastric mucous membrane to secrete. It is probable, therefore, that these substances are absorbed in small quantities by the pyloric mucous membrane, in which they produce a substance, "gastrin," the presence of which in the blood stimulates the gastric glands to secrete.

Gastric juice begins to flow about five minutes after the commencement of a meal as a result of psychical influences. Salivary digestion of starch and peptic digestion of protein soon give rise to substances, which increase the secretion of gastric juice by acting as chemical stimulants. The psychical secretion is essential for the digestion of native proteins, as it gives rise to the products of digestion which are capable of stimulating a further secretion,

whereas the proteins themselves have no such action. In the case of meat, however, the extractives cause a secretion of gastric juice, which can digest the protein even in the absence of any psychical secretion.

Fat taken before, with or after food diminishes the secretion of gastric juice, whether it be produced by psychical or chemical stimulation. The inhibition is reflex and occurs from the duodenum as well as the stomach. The presence in the duodenum of soap, produced by the action of pancreatic juice on fat, excites a secretion of gastric juice, so that in the later stages of digestion the inhibiting effect of fat may be to some extent neutralized. Sodium bicarbonate also inhibits the secretion of gastric juice, but sodium chloride is without action.

Hydrochloric alone among acids has a weak inhibitory action on the secretion of gastric juice, whilst some organic acids, such as butyric acid, act as powerful stimulants. The inhibitory action of hydrochloric acid tends to prevent an excessive quantity of free hydrochloric acid collecting in the stomach, and the stimulating action of butyric acid arrests its own formation, as hydrochloric acid inhibits butyric acid fermentation.

**Free, Combined, and Active Hydrochloric Acid.**—Hydrochloric acid may be present in the stomach in three forms—free, combined with proteins or other nitrogenous bases, such as creatin, and combined with inorganic bases in the form of neutral salts. As most of that combined with inorganic bases is derived directly from the food, the amount of hydrochloric acid which is free and in combination with organic bases approximately represents the amount secreted in the gastric juice. Combination with organic bases does not prevent the acid taking an active part in protein digestion; consequently the amount of free hydrochloric acid together with that combined with organic bases is known as the "active" hydrochloric acid. This gives an indication of the secretory activity of the stomach and the digestive power of the gastric juice far better than the quantity of free hydrochloric acid, as the latter depends upon the quantity of protein present, and may therefore be absent even when the quantity of active hydrochloric acid is normal.

A specimen of pure gastric juice cannot under ordinary conditions be obtained, and all that it is possible to analyze is the mixture of gastric juice with the food which stimulated its secretion. Variations in the percentage of hydrochloric acid depend, therefore, as much upon the relative volumes of gastric juice and of food present at the moment of examination as upon the strength of the gastric juice itself. The percentage of active hydrochloric acid present after a test meal might conceivably be greater than normal owing to the secretion of an abnormally strong gastric juice or an abnormally large quantity of juice, or to excessive motor activity

causing the food to pass with unusual rapidity into the duodenum, whilst the gastric juice was still being secreted. It will be shown later that the most important of these factors is the quantity of juice secreted.

The quantity of ferments contained in the gastric juice varies considerably according to the nature of the stimulus which called it forth. Though pure gastric juice almost always contains approximately the same quantity of acid, it contains more or less ferment according to the nature of the food and the conditions under which it is eaten.

1. **Excessive Secretion of Gastric Juice—Hyperchlorhydria, Hypersecretion.**—Until recently it was generally believed that *hyperchlorhydria*—the secretion of gastric juice containing an abnormally high percentage of hydrochloric acid—was the commonest form of excessive secretory activity. But observations made on the secretion in gastric fistulæ both in animals and human beings have shown that it is impossible to increase the percentage of hydrochloric acid by any experimental means, though the quantity secreted can be readily influenced. It was found, moreover, that normal undiluted human gastric juice contains between 0·35 and 0·55 per cent. HCl, whilst the normal percentage of active hydrochloric acid after a test breakfast is from 0·1 to 0·2, and 0·55 is a greater percentage than that found in the severest case of "hyperchlorhydria." It is uncertain whether gastric juice containing an excessive percentage of hydrochloric acid is ever excreted, and whether so-called hyperchlorhydria is not always due to hypersecretion.

The secretion of an excessive quantity of gastric juice—hypersecretion—may occur (*a*) most frequently during digestion, (*b*) in paroxysms independently of digestion, and (*c*) continuously.

(*a*) *Digestive Hypersecretion.*—In digestive hypersecretion an abnormally large amount of normal gastric juice is secreted in response to the stimulus of a meal. The volume of gastric contents removed after a test meal is therefore excessive, and the percentage of active and of free hydrochloric acid is increased owing to the relatively high proportion of gastric juice compared with food in the gastric contents.

The amount of gastric juice secreted as a result of a given stimulus varies considerably in different individuals and in different nations, the chief determining factor probably being the diet which is habitually taken; and some perfectly healthy people have what may be termed digestive hypersecretion, although they suffer from no gastric symptoms.

The commonest cause of slight hypersecretion is the chronic irritation caused by habitual overeating and insufficient mastication, especially if much indigestible food, strong tea or alcohol is consumed, or much tobacco smoked. Gastric hypersecretion may

therefore precede or accompany the early stages of chronic catarrhal gastritis. In some cases it is only the initial secretion which is excessive; though the gastric glands are excited to activity with abnormal ease, they become rapidly exhausted, so that the total secretion may be deficient.

The indigestion which frequently accompanies chlorosis is generally associated with hypersecretion. This is perhaps the result of irritation by the excess of tea and indigestible carbohydrate food, which is commonly consumed by chlorotic girls.

The most important cause of more severe digestive hypersecretion is ulceration of the stomach and duodenum. Only in very chronic cases of gastric and duodenal ulcer may hypersecretion be absent, the associated catarrh interfering with the excessive secretion of gastric juice. It has been suggested that the hypersecretion is primary and the cause of the ulceration. This is probably not the case, although there is no doubt that a high percentage of active hydrochloric acid tends to prevent an ulcer from healing. Observations made on one of Pawlow's dogs, in which an ulcer formed spontaneously in the gastric cul-de-sac, showed that during its development the quantity of gastric juice became more and more excessive, the flow being finally three or four times greater than normal, but the percentage of hydrochloric acid remained unaltered. The psychical secretion which occurs in the first hour after a meal was unaltered, the hypersecretion being confined to the subsequent hours. The hypersecretion is therefore probably due to the irritation of the surface of the ulcer producing an excessive reflex secretion. Reflex hypersecretion may also occur in diseases of the gall-bladder and the appendix.

(*b*) *Paroxysmal Hypersecretion.* — Paroxysmal secretion of an excessive quantity of gastric juice for a few hours or for several days independently of the presence of food in the stomach constitutes one form of the gastric crises of tabes. A similar condition may occur in association with headache in some cases of migraine.

(*c*) *Continuous Hypersecretion.*—When a gastric or duodenal ulcer involves the pyloric canal, the secretion of gastric juice becomes continuous; meals cause an increase in the flow, but it does not cease even when every trace of food has left the stomach. In such cases from 50 to 1,000 c.c. of pure gastric juice are found in the stomach before breakfast. During meals the gastric juice is diluted and most of the hydrochloric acid combines with the protein of the food, but in the intervals there is nothing but the gastric mucus and the mucus and sodium bicarbonate of the saliva with which it can combine. Consequently a higher percentage of free hydrochloric acid and of active hydrochloric acid is present in the intervals between meals than immediately after meals, although the strength of gastric juice secreted probably remains constant.

2. **Deficient Secretion of Gastric Juice—Hypochlorhydria, Hyposecretion.**—Deficient secretory activity may manifest itself in the secretion of an abnormally small quantity of normal gastric juice (hyposecretion), or of a juice containing an abnormally small percentage of hydrochloric acid (hypochlorhydria). It is generally impossible to distinguish between these two conditions with any certainty, so that they will have to be discussed together.

Hyposecretion of gastric juice naturally results in a diminution in the quantity of both hydrochloric acid and ferments present in the stomach. Hypochlorhydria is also generally accompanied by a corresponding diminution in the amount of ferments present in the gastric juice. When no hydrochloric acid is secreted (*achlorhydria*), the gastric ferments are greatly diminished, but are very rarely absent entirely (*achylia*), although they are inactive unless hydrochloric acid is added to them.

The quantity of hydrochloric acid in the stomach diminishes in the later years of life, free hydrochloric acid being absent from the gastric contents in more than 30 per cent. of individuals over the age of fifty. In all diseases which result in malnutrition and in acute fevers free hydrochloric acid is generally diminished or absent and the active acid deficient. In Addison's anæmia (pernicious anæmia) free hydrochloric acid is absent and active hydrochloric acid very much reduced, and the ferments may be completely absent. In these conditions the principal change is in the quantity of juice secreted, although it is probable that the percentage of hydrochloric acid is also diminished, especially in Addison's anæmia. Hyposecretion also occurs when for any reason the quantity of salt or water present in the body is less than normal, but the percentage of hydrochloric acid remains unaltered.

In certain organic gastric diseases, such as gastritis, lardaceous disease and cancer, true hypochlorhydria occurs with or without hyposecretion. Free hydrochloric acid is completely absent and active hydrochloric acid greatly diminished in acute gastritis. Severe chronic gastritis may result in partial atrophy of the mucous membrane with degeneration of the oxyntic or acid-secreting cells. This leads to a diminished secretion of hydrochloric acid, some of which also combines with the mucus which is always present in excess, so that free hydrochloric acid may be absent. In cancer of the stomach there is invariably a diminution in the quantity of active hydrochloric acid, and free hydrochloric acid is generally absent. This is due partly to the associated catarrh, partly to deficient psychical secretion resulting from anorexia, and partly to some specific action. The nature of the latter is uncertain, but cancerous tissue contains a thermolabile substance, admixture with which diminishes the activity of gastric juice.

In the condition known as *primary achylia gastrica*, the gastric mucous membrane secretes no hydrochloric acid or ferments, as a

result probably of a congenital abnormality of the mucous membrane.

The secretion of an adequate quantity of gastric juice depends largely upon the stimulating influence of a healthy appetite and the pleasure derived from the sight, smell and taste of a good meal, for in the absence of the initial psychical secretion the subsequent chemical secretion is greatly diminished. When, therefore, food is eaten quickly with a preoccupied mind, or when it is distasteful or served under unpleasant conditions, or when the tongue is furred and the sense of taste impaired, the psychical stimulus is deficient, and the initial secretion of appetite juice does not occur. The hyposecretion which is frequently present in neurasthenia is mainly due to deficient psychical secretion of gastric juice.

Reflex inhibition of the flow of gastric juice occurs in the same conditions which cause inhibition of peristalsis.

**Results of Abnormalities in Gastric Secretion.**—When an excessive quantity of active hydrochloric acid is present in the stomach, salivary digestion ceases unduly early, with the result that an excessive quantity of undigested starch reaches the intestine. When, on the other hand, there is a deficiency of active hydrochloric acid, salivary digestion continues for an unusually long period, and in achlorhydria it continues for the whole period during which the food remains in the stomach.

Protein digestion occurs with great rapidity in hypersecretion, and abnormally slowly when the quantity of acid is deficient. In the former condition a large proportion of the protein in the food is dissolved in the stomach; in the latter most of it is digested in the intestine.

An important function of the hydrochloric acid of the gastric juice is to soften and dissolve connective tissue. In hypersecretion this occurs with great rapidity, the muscle fibres and fat being set free, so that the former is quickly exposed to the digestive action of the gastric juice. In hyposecretion and hypochlorhydria, connective tissue is only slowly dissolved, so that meat is insufficiently broken up, and its digestion, which is deficient owing to feeble peptic activity, is still further impeded. As the gastric juice is the only secretion which has the power of dissolving connective tissue, the large particles of meat, which reach the intestine when the secretion of hydrochloric acid is deficient, are excreted unchanged in the fæces after irritating the mucous membrane during their passage through the alimentary canal.

The effect of variations in gastric secretion on bacterial activity is considered in Section IX.

### B. Gastric Mucus.

The mucous membrane of the stomach is always covered by a very thin layer of mucus, which protects it from chemical, thermal and mechanical irritants, from the invasion of bacteria and from autodigestion by gastric juice. During digestion its secretion is increased, but the quantity is always so small and it is so thoroughly mixed with the food that it requires special methods to recognize its presence in the gastric contents.

Irritation of the stomach by substances such as alcohol and silver nitrate causes the rapid secretion of a large quantity of mucus, the secretion of gastric juice being at the same time diminished. If the irritation is not repeated, the secretion on the following day is normal. The secretion of mucus by the surface epithelial cells protects the glands from injury, as it dilutes and in some cases combines with the irritant, and at the same time prevents its access to the mucous membrane. If the irritation is not repeated, the secretion on the following day is normal. But when the irritation is more profound or more prolonged, catarrh develops, inflammation of the mucous membrane being associated with deficient secretion of gastric juice and excessive secretion of mucus by the surface epithelium, the cells of which are in a state of great activity and may even be increased in number.

A condition of *gastromyxorrhœa* has been described, in which excessive mucus is secreted either continuously or in paroxysms quite independently of any catarrhal inflammation. It is regarded as analogous to muco-membranous colitis, but so few observations have been made on the subject that it is still uncertain whether the condition really occurs.

An apparent increase in the quantity of mucus occurs when peptic digestion is deficient, as, although the normal quantity of mucus is secreted, a smaller proportion than usual is dissolved in the gastric juice.

It is uncertain whether such a condition as *amyxorrhœa* exists, in which the secretion of mucus in the stomach is deficient. Some have regarded it as a predisposing cause of gastric ulcer, the mucous membrane being inadequately protected against autodigestion by gastric juice and invasion by bacteria, the quantity of free hydrochloric acid present being simultaneously increased owing to the absence of mucus with which it can combine.

## V. THE MOTOR FUNCTIONS OF THE INTESTINES.

In addition to the peristaltic waves, which propel the contents of the small intestine slowly towards the cæcum, another and equally important type of movement occurs, which has been called "segmentation." The small intestine is divided into short seg-

ments, at first uniform in thickness, which then become constricted in their centre. The constriction increases until each segment is more or less completely divided into two, the halves of neighbouring segments joining together. Each new segment now undergoes a similar division, neighbouring halves again joining together, so that segments similar to the original ones are once again formed, the segmentation continuing in one place at the rate of ten divisions in a minute and a half. The function of segmentation is to mix the food thoroughly with the bile, pancreatic juice and intestinal juice, and at the same time to bring every portion into frequent contact with the absorbing mucous membrane.

The gastric contents begin to pass through the pylorus immediately after the commencement of a meal and reach the cæcum in about four hours, the average rate at which the contents of the small intestine travel being about one inch per minute. Owing to the existence of the strong ileo-cæcal sphincter, no mixing takes place between the contents of the small and the large intestine, and material which has once reached the cæcum never returns into the ileum.

Until about four hours after breakfast the cæcum contains nothing but gas and sometimes a small quantity of fæcal matter sticking to its mucous membrane. The fluid contents of the ileum, containing the unabsorbed part of the meal and the digestive juices, then begin to arrive. A considerable amount of water is absorbed in the colon, as about 350 grammes of fluid material pass through the ileo-cæcal sphincter in a day, whereas the weight of the fæces averages 135 grammes. Small quantities of sugar, fat and coagulable protein and of the products of their digestion reach the cæcum; they are completely absorbed in the large intestine. Most of the absorption of water and nutrient material in the large intestine takes place in the cæcum and ascending colon; some also occurs in the transverse colon; and the normal firm consistence of the stool is finally attained in the pelvic colon, where the fæces are retained until the act of defæcation occurs.

When sufficient material has accumulated in the cæcum and ascending colon to produce slight distension, peristaltic waves, occurring much less frequently and moving much more slowly than in the small intestine, carry the contents towards the rectum. There is no evidence that the antiperistalsis, which has been observed in the colon of certain animals, ever occurs in man. The average periods required by the residue of a meal to reach the different parts of the colon are four and a half hours to the cæcum, six and a half hours to the hepatic flexure, nine hours to the splenic flexure, eleven hours to the iliac colon, and thirteen hours to the commencement of the pelvic colon (Fig. 29).

The activity of the whole of the large intestine during defæcation causes some of the fæces in the distal half of the transverse colon

to enter the descending colon, from which it is evacuated together with all the fæces already present between the splenic flexure and the anus. Hence if food is taken nine hours before defæcation, some of its residue is present in the stool. If, however, it is taken less than nine hours before defæcation, none of it can reach the splenic flexure by the time the act occurs and be present in the fæces. It continues to advance until it reaches the pelvic colon, where it remains until the next act of defæcation. If this occurs twenty-four hours after the previous act, and if the latter takes place about eight hours after a meal, the residue of the meal must occupy thirty-two hours in its passage through the alimentary canal. Thus if the bowels are opened once a day, the interval between a meal and the excretion of its residue varies approxi-

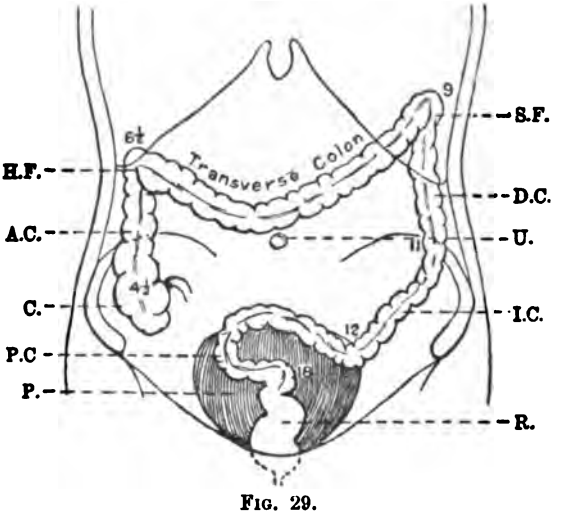



FIG. 29.

The numbers in this and succeeding figures represent the hours which elapsed after a bismuth meal before the different parts of the colon were reached.

mately between nine and thirty-two hours, the time depending upon when the meal is eaten and the hour of defæcation.

The intestinal movements depend upon local reflexes, which are produced by mechanical and chemical stimuli. Irritation of any part of the intestine gives rise to contraction above and relaxation below. This combination of a proximal contraction with a distal relaxation causes the contents to move onward, with the result that a wave of contraction, preceded by a wave of relaxation, passes down the intestine. Such a compound wave constitutes true peristalsis. Mechanical stimulation of the intestine is produced by the direct action of indigestible and undigested remnants of food, and by the distension they produce when mixed with the

digestive juices. Fragments of vegetable food, consisting of indigestible cellulose, together with starch and protein, which have escaped digestion owing to their covering of cellulose, are the most important of the articles of diet which mechanically stimulate the intestinal movements. When the food is insufficiently chewed, lumps of undigested meat act in the same way.

Chemical stimulation of the intestine is produced by certain constituents of the food and by the products of their digestion and bacterial decomposition. Sugar, whether present in the food or produced in the course of digestion of starch, which is itself inactive, stimulates peristalsis in the small intestine, but not in the colon, in which, however, it is only present in very small quantities. All parts of the intestine are stimulated by organic acids, such as acetic, butyric, tartaric, citric and lactic acids, which are either produced in the intestines by the fermentation of carbohydrates or are already present in vegetables and fruit. Undigested animal food produces no chemical stimulation, except for the extractives it contains, and these affect the small intestine only. Peptone acts as a feeble stimulant in the small intestine, and the amino-acids produced at a later stage of digestion act on all parts of the intestines. Of the products of the putrefaction of proteins in the colon, indol, phenol and skatol are inactive. Oil stimulates peristalsis in the small intestine, and the products of its digestion and bacterial decomposition—glycerine, fatty acids and soaps—are comparatively powerful stimulants, which act on the colon as well as on the small intestine. Carbon dioxide and marsh gas, produced by fermentation of carbohydrates, and sulphuretted hydrogen, produced by putrefaction of proteins, actively stimulate all parts of the intestines. Bile is a weak stimulant to peristalsis in the colon, but not in the small intestine. Pancreatic juice, water and normal saline solution at the body temperature have no action.

As both the mechanical and the chemical stimulation of the intestinal movements is greater with a vegetable than with a meat diet, peristalsis is more vigorous in herbivorous than in carnivorous animals and in vegetarians than in people who take a mixed diet.

The entrance of food into the stomach acts as a powerful stimulus to intestinal movements. X-ray observations have shown that there may be more progress in the passage of fæces through the colon during the hour in which dinner is eaten than in the previous four hours. This is mainly due to reflex stimulation of the intestinal movements, but it is undoubtedly aided by the psychical effect produced by the sight, smell and taste of food. The intestinal movements are increased by exercise, owing to mechanical stimulation by the variations in the intra-abdominal pressure, caused by the increased respiratory excursions of the diaphragm and by the contraction of the abdominal and psoas and iliacus muscles.

**The Nervous Control of the Gastric and Intestinal Movements.**—The muscular coat of the stomach and small intestine receives through the splanchnic nerves sympathetic fibres, which originate in the lower dorsal and upper lumbar region of the spinal cord and have their cell-station in the solar plexus; the sympathetic nerve supply to the colon originates in the lower lumbar region, the cell-station being in the inferior mesenteric ganglion. The stomach and small intestine are also supplied with fibres from the vagi; the large intestine is supplied through the pelvic nerves with fibres from the sacral cord, which are unconnected with the sympathetic system and are physiologically equivalent to the vagi. The vagal and sacral fibres end in connection with ganglion cells situated between the circular and longitudinal muscular layers, where they constitute Auerbach's plexus.

Stimulation of the splanchnic nerves diminishes the tone of the gastric and intestinal muscles and inhibits their movements, whereas stimulation of the vagi, or, in the case of the colon, the pelvic nerves, increases their tone and renders their movements more active after temporarily inhibiting them. Stimulation of the vagi also increases the tone of the pylorus, whilst stimulation of the splanchnic nerve, inhibits it. The ileo-cæcal sphincter is kept in a condition of moderate tonic contraction by the splanchnic nerves; when these are cut, it becomes permanently relaxed and the contents of the small and large intestines mix freely with each other. Direct stimulation of the splanchnic nerves causes the sphincter to contract tightly, at the same time as the movements of the rest of the intestine are inhibited. Stimulation of the vagi and pelvic nerves have no influence on it.

In spite of the fact that they possess this double nerve-supply, peristalsis occurs in excised stomachs and intestines, which have been kept moist and warm, and the tone and movements of the stomach and intestines and the pyloric reflex remain normal for months after division of the splanchnic nerves or both vagi. Separated strips of intestinal muscle are only capable of spontaneous rhythmical contractions if Auerbach's plexus is removed with them; otherwise the refractory period, which normally follows activity, is abolished, so that a continuous stimulus produces tetanus instead of rhythmical contractions. It is therefore probable that the motor activity of the stomach and intestines depends largely on reflexes, which have their centre in the nerve cells of Auerbach's plexus, although there is no doubt that it can be directly and reflexly influenced by the central nervous system.

Painful stimulation of sensory nerves, anger and excitement inhibit gastric and intestinal movements, the inhibitory impulses being conveyed by the splanchnic nerves.

**Defæcation.**—Owing to the acute angle formed at the pelvi-rectal flexure, the further passage of fæces along the colon is obstructed

at this point (Fig. 30). Consequently the pelvic colon becomes filled with fæces from below upwards, and the rectum remains empty until immediately before defæcation. In individuals, whose bowels are opened regularly every morning before breakfast, the entry of fæces into the rectum gives rise to the sensation of fulness, which leads to the desire to defæcate and may be termed the "call to defæcation." The passage of fæces from the pelvic colon into the rectum is the result of active peristalsis in the former, brought about reflexly by various stimuli, the chief of which is the taking of food at breakfast into the empty stomach. The same effect is produced by a cold bath, by the muscular activity involved in getting up and dressing, and by drinking a glass of cold water before breakfast. If no desire to defæcate is felt at the proper time, voluntary contraction of the abdominal muscles and diaphragm may force some fæces into the rectum, the call to defæcation being thus voluntarily produced.

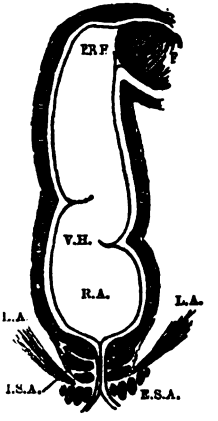



FIG. 30.—DIAGRAM OF RECTUM, SHOWING PELVI-RECTAL FLEXURE (*P.R.F.*), FÆCES IN THE PELVIC COLON (*F*), HOUSTON'S VALVE (*V.H.*), RECTAL AMPULLA (*R.A.*), LEVATOR ANI (*L.A.*), INTERNAL SPHINCTER (*I.S.A.*), AND EXTERNAL SPHINCTER (*E.S.A.*).

The rectum is insensitive to tactile and chemical stimulation. The call to defæcation cannot, therefore, be due to the mere contact of fæces with the rectal mucous membrane. Observations made by inflating a balloon introduced in the rectum show that a sensation of fulness, identical in character with the natural call to defæcation, is felt when it is distended. Consequently the entrance of fæces into the upper part of the rectum produces the call to defæcation, which increases in intensity as more fæces enter and when the most advanced portion reaches and distends the more sensitive ampulla.

If a response is not at once made to the call to defæcation, the desire to defæcate passes away. This is due to the relaxation of tone, which occurs in the muscular coat of the rectum after it has been subjected to a certain degree of tension for a short period. The call to defæcation only returns after a further quantity of fæces has entered the rectum and produced a rise in intrarectal pressure. This may occur after any meal, but most frequently only after breakfast on the following morning.

The call to defæcation having occurred as a result of the entry of a small quantity of fæces into the rectum, the act itself is started by the increase in intra-abdominal pressure, which is caused by the voluntary contraction of the diaphragm and the muscles of the abdominal wall. The abdominal muscles act more by offering a firm resistance than by actually diminishing the capacity of

the abdominal cavity, the chief factor in bringing about the latter being the contraction of the diaphragm, which is maintained in its dependent position by the closure of the glottis at the end of inspiration. The tonic contraction of the muscles of the pelvic floor resists the pressure from above, and allows the other voluntary muscles of defæcation to create the necessary rise in intra-abdominal pressure. This is further increased by the flexion of the spine with the resulting approximation of the sternum to the pubes, and by the pressure of the thighs on the abdominal wall, when the natural crouching position is assumed. The rise in intra-abdominal pressure causes more fæces to enter the rectum, which consequently becomes distended.

The distension of the rectum gives rise to the reflex act, which completes the process of defæcation. This consists in strong peristaltic contractions of the whole of the colon, contraction of the voluntary muscles enclosing the abdominal cavity and relaxation of both anal sphincters. Though the whole process may be entirely involuntary, under normal conditions it is assisted by the voluntary contraction of the diaphragm and abdominal muscles, and by voluntary relaxation of the external anal sphincter.

The fæcal mass is forced through the relaxed anal canal by the contraction of the intestine and the raised intra-abdominal pressure. Its final expulsion from the rectum is helped by the voluntary action of the levator ani muscles, which draw the anal canal upwards over it as it is foreed downwards through the relaxed sphincter. Finally they clear out the last traces of fæces by contracting tightly behind them, so as to constrict the lowest part of the rectum.

The rectum receives a similar double nerve-supply to that of the colon. The lower lumbar nerves contain fibres, which pass through the sympathetic chain to the inferior mesenteric ganglia, where they are connected with nerve cells, from which fibres pass in the colonic nerves to the colon and in the hypogastric nerves to the rectum and internal sphincter ani. In addition, fibres leave the conus terminalis, chiefly by the third sacral nerve root, and pass by the pelvic nerves (or nervi erigentes) to the colon and the internal sphincter, in the immediate neighbourhood of which is situated the inferior hæmorrhoidal plexus, where they have their ganglion cells. Stimulation of both the lumbar and the pelvic nerves leads to contraction of the rectum and inhibition of the internal sphincter. The fourth sacral nerve supplies the voluntary external sphincter ani and the levator ani muscles, and its stimulation results in their contraction.

The external sphincter ani, being a voluntary muscle, receives its nerve-supply by fibres which originate in cells situated in the grey matter of the conus terminalis; the latter therefore contains the centre for the reflex contraction of the sphincter, which occurs when the anus is irritated. In diseases and injuries of the spinal

cord above the lumbar region the tone and reflex contraction of the external sphincter are unaffected or only temporarily impaired, but it is no longer possible by an effort of will to contract the muscle and prevent the escape of fæces when the rectum is getting rid of its contents. If, on the other hand, the lowest segment of the spinal cord is destroyed, the external sphincter becomes completely relaxed and no longer contracts when the anus is irritated.

The muscular coat of the colon and rectum and the internal sphincter ani are composed of involuntary muscle fibres, and their nerve-supply originates from ganglion cells of peripheral nerve plexuses and not from cells in the spinal cord. It is probable that these ganglion cells form the centre for the reflex defæcation, which occurs when the rectum is distended or irritated, for disease or injury to the spinal cord produces no more disturbance in defæcation when it is situated in the conus terminalis than when it is above the lower lumbar region. In both conditions the voluntary impulses from the brain, which normally assist or inhibit the reflex act of defæcation, are cut off, and the rectum and anal canal are completely anæsthetic, the accumulation of fæces in the rectum and their expulsion from the anus producing no sensation. But the reflex act of defæcation remains intact, and in spite of the patulous condition of the external sphincter when its spinal centre is destroyed, fæces do not continually escape from it, but are expelled periodically whenever the distension of the rectum calls forth the defæcation reflex, in the same way as when the lesion is higher in the cord.

When defæcation ceases to be under the control of the will, more or less constipation always results, as the patient does not experience the call to defæcation, which normally occurs as soon as a small quantity of fæces reaches it from the pelvic colon. The voluntary acts, which this sensation normally calls forth, do not occur, so that a considerable quantity of fæcal matter gradually collects in the rectum, where it becomes dry and hard from the absorption of water before the reflex is excited. The reflex is then generally insufficiently strong to expel the hard masses of retained fæces, and cumulative constipation tends to occur. In order to avoid this purgatives are often given, with the result that fluid fæces reach the rectum. If this occurs in cases in which the conus terminalis is diseased, genuine fæcal incontinence results, as the tonic action of the external sphincter, which should prevent the escape of the rectal contents, is absent.

The old doctrine of a defæcation centre in the conus terminalis is to some extent correct, as the complete reflex includes the contraction of the abdominal and levator ani muscles and the relaxation of the external sphincter, these being voluntary muscles under the control of nerve cells, situated in the spinal cord and not in the peripheral plexuses. Hence the peripheral reflex which occurs when the conus terminalis is thrown out of action is

incomplete, although the abdominal muscles and diaphragm may still help in defæcation as a result of an effort of will. It is probable that the hæmorrhoidal plexus normally acts as a subordinate centre for defæcation, which is under the control of the centre in the conus terminalis, and this is in turn governed by exciting and inhibitory influences, which reach it from the brain by way of the spinal cord.

### A. Changes in Tone.

The lumen of the transverse and descending colon is normally very much less than that of the cæcum and ascending colon, but in atony, due to such local conditions as chronic dysentery, the

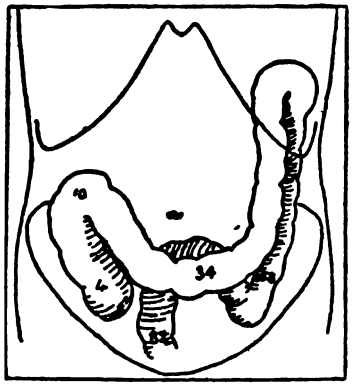


FIG. 31.—ATONIC DILATATION OF THE COLON DUE TO DYSENTERY.

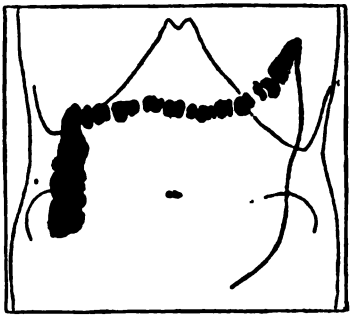


FIG. 32.—SPASTIC CONDITION OF THE DESCENDING ILIAC COLON IN A CASE OF MUCO-MEMBRANOUS COLITIS.

lumen of the whole colon may be uniformly enlarged (Fig. 31). On the other hand, in so-called *spastic constipation* various segments of the colon are abnormally contracted, the descending colon being the part most frequently affected (Fig. 32).

### B. Constipation.

**Varieties and Definition of Constipation.**—The abnormal action of the bowels in constipation may manifest itself in three different ways: defæcation may occur with insufficient frequency, the stools may be insufficient in quantity, and they may be abnormally hard and dry. To have one action of the bowels a day is often regarded as the only normal condition, but it is really nothing more than a question of convenience, being found to suit the habits and diet of the majority of civilized people. It is, indeed, not very rare to find people in perfect health, who defæcate regularly two or three times a day, and others who obtain an evacuation once in two, three or more days, without suffering the smallest ill effects.

Such individuals, so long as defæcation, when it does occur, is complete, can no more be regarded as diseased than those otherwise normal people whose hearts beat only forty or fifty times a minute. The majority, however, although they may suffer no inconvenience for a considerable time, finally develop symptoms due to fæcal accumulation, gradually increasing quantities of fæces being retained. For practical purposes, therefore, an individual may be considered constipated if his bowels are not opened at least once in every forty-eight hours. A less frequently recognized variety of constipation is that known as "cumulative constipation," in which insufficient fæces are excreted, although the bowels may be opened every day, a condition analogous to retention of urine with overflow. Lastly, the amount of fæces formed

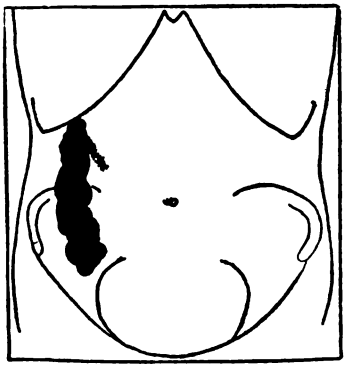


FIG. 33.—INTESTINAL CONSTIPATION.

Tracing taken twenty-four hours after a bismuth meal, showing the bismuth collected in the cæcum and ascending colon.

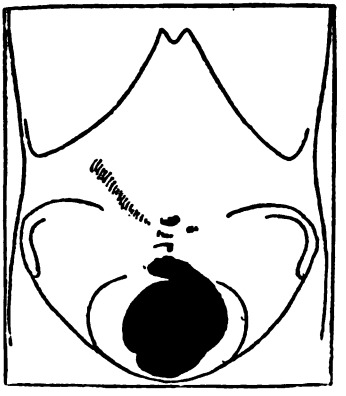


FIG. 34.—DYSCHEZIA.

Tracing taken twenty-four hours after a bismuth meal, showing all the bismuth collected in a dilated rectum, with the exception of a small quantity in the transverse colon.

may be normal and the bowels may be opened daily, yet the fæces are abnormally hard and dry owing to prolonged retention before excretion.

A more scientific classification than that just considered depends upon which of the two great physiological processes, which maintain the regular action of the bowels, is deranged. These two processes are, firstly, the passage of the residue of the food from the stomach to the pelvic colon, and, secondly, the complete evacuation of the pelvic colon at proper intervals. In the first class of constipation the passage through the intestines is delayed, whilst defæcation is normal; this may be called *intestinal constipation* (Fig. 33). In the second class there is no delay in the arrival of the fæces in the pelvic colon, but their final excretion is not adequately performed; for this I have adopted the name *dyschezia* (Fig. 34). The two

forms of constipation may co-exist in the same patient, but in the majority of cases one is much more prominent than the other. There is an important form of constipation, which is due to insufficient formation of fæces; this cannot strictly be included under the head of either intestinal constipation or dyschezia, and must therefore be considered separately.

In normal defæcation all the contents of the large intestine beyond the splenic flexure are excreted. As the greatest period which should elapse after a meal before the splenic flexure is reached is sixteen hours, some of the residue of a meal taken eight hours after defæcation should be excreted at the next defæcation in individuals whose bowels are opened punctually every twenty-four hours. If, however, the bowels are only opened on alternate mornings—a condition which is not necessarily pathological—forty hours would elapse instead of sixteen before some of the residue of the meal would be excreted. Constipation may therefore be defined as a *condition in which none of the residue of a meal, taken eight hours after defæcation, is excreted within forty hours.* This definition embraces the clinical varieties of constipation, in which defæcation occurs with insufficient frequency and in which the stools are insufficient in quantity or are abnormally hard and dry, and the pathogenetic classes, to which I have referred as intestinal constipation and dyschezia.

### 1. Intestinal Constipation.

Delay in the passage of fæces through the intestines is due to (1) the motor activity of the intestines being deficient, or (2) the force required to carry the fæces to the pelvic colon being excessive. Apart from organic obstruction, the delay in either case is generally confined to the large intestine beyond some point distal to the hepatic flexure, this being the situation where the intestinal contents begin to be more or less solid, so that additional force is required for their propulsion. Moreover, an increasing resistance is offered to the progress of the intestinal contents as they pass towards the pelvic colon, because the lumen of the cæcum and ascending colon is much greater than that of the transverse colon, and the latter diminishes in size as it approaches the splenic flexure, the diameter of the descending colon being smaller than that of any other part of the large intestine.

(1) *Constipation due to Deficient Motor Activity of the Colon.*—The motor activity of the colon may be deficient owing to (*a*) weakness of the musculature, (*b*) deficient reflex activity, (*c*) inhibition, and (*d*) uncontrolled and irregular action.

(*a*) *Weakness of the Intestinal Musculature.*—This may be due to congenital hypoplasia, which is the cause of the constitutional constipation, from which several members of a family may suffer

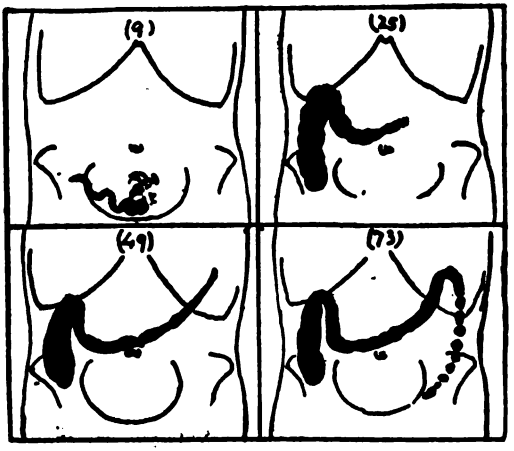



FIG. 35.—CONSTITUTIONAL CONSTIPATION.
Tracings taken at different hours after a bismuth meal.

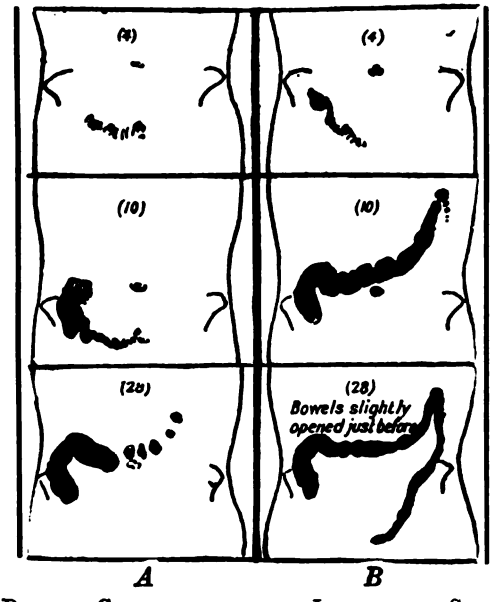



FIG. 36.—*A*, DIETETIC CONSTIPATION DUE TO INSUFFICIENT STIMULATING FOOD; *B*, FROM THE SAME PATIENT WHILST TAKING A PROPERLY MIXED DIET.
Tracings taken at different hours after a bismuth meal.

(Fig. 35); acquired hypoplasia, which is the cause of senile constipation and the constipation which may follow such local diseases as dysentery; functional insufficiency without structural change, as

in chlorosis, acute fevers, and the cachexia of cancer and tuberculosis; overdistension by flatulence; and fatty infiltration in extreme cases of obesity.

(*b*) *Deficient Reflex Activity.*—The reflexes which maintain intestinal activity may be deficient owing to the stimulation being too weak, on account of lack of mechanical and chemical stimulants in the food (Fig. 36), or want of exercise. They are also deficient when the excitability of the mucous membrane of the colon is impaired as a result of catarrh and of long-continued irritation by purgatives.

(*c*) *Inhibition of the Motor Activity of the Intestines.*—The inhibitory fibres of the sympathetic nerves may be stimulated directly, as in lead-poisoning (Fig. 37), centrally by depressing emotions, and reflexly in painful diseases of the abdominal viscera. As the inhibitory nerves of the small intestine and colon come from adjacent parts of the spinal cord and have their cell-stations in closely related sympathetic ganglia, delay occurs in the small intestine as well as in the colon in cases of constipation which result from inhibitory impulses. Temporary constipation often follows depressing emotions, and many constipated people find that the difficulty they experience in getting their bowels to act increases whenever they are worried or annoyed. Reflex inhibition of intestinal movements is the cause of the constipation which is frequently produced by the painful stimulation of sensory nerves in diseases and injuries of any part of the body, but particularly of the abdomen and pelvic viscera. A blow in the abdomen or contusion of the testicles may produce such profound inhibition of the intestinal movements that death results, although nothing abnormal is found at the autopsy. Post-operative ileus, when not the result of peritonitis, is due to the reflex inhibition which results from handling the stomach and intestines, especially if the mesentery be stretched. The intestinal stasis, which occurs on perforation of an abdominal viscus, is due primarily to the irritation of the peritoneum producing reflex inhibition of the intestinal movements and spasm of the ileocæcal sphincter; the peritonitis, which develops later, increases the constipation by the directly injurious effect of the inflammation, which spreads to the muscular coat of the intestines.

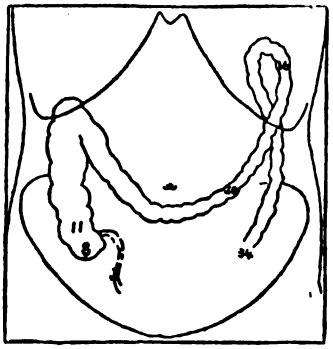


FIG. 37.—LEAD-POISONING.

(*d*) *Uncontrolled and Irregular Motor Activity—Spastic Constipation.*—Constipation may be associated with spasm, which is produced reflexly when an irritant is present in the colon, especially if the patient

has an abnormally excitable nervous system. The most common irritant is hard fæces, which accumulate as a consequence of the constipation generally present in neurasthenic individuals. It is improbable that the resulting aggravation of the constipation is due alone to the mechanical obstruction offered by the contracted intestine, as visible and palpable peristalsis and other signs of intestinal obstruction are never present. A more important factor appears to be the absence of the normal propulsive activity of the intestine, which is replaced by irregular spasmodic contractions of some parts, whilst others remain inactive. Similar spasmodic contractions of the intestines occur in cases of lead-poisoning, in which constipation is associated with colic; in such cases the spasm is probably the result of direct irritation of the vagus.

(2) *Constipation due to Excessive Force required to carry the Fæces to the Pelvic Colon.*—The work to be done by the intestinal musculature is excessive (*a*) whenever the bulk or consistence of the fæces offers more than the normal degree of resistance, and (*b*) whenever there is any narrowing of the intestinal lumen.

(*a*) The *fæces may be abnormally bulky* in big eaters, who habitually bolt their food, and in infants fed on a diet of undiluted cow's milk. *Abnormal dryness and hardness* may be due to an insufficient supply of water, excessive loss of water in the urine in diabetes and in the sweat after hard exercise in hot weather and excessive absorption of water from the intestines.

(*b*) *A diminution in the intestinal lumen*, which causes constipation by obstructing the passage of fæces to the pelvic colon, may be due to organic stricture, pressure exerted from without, and intussusception. A kink at the splenic flexure is in rare cases one factor in the constipation, which is frequently associated with visceroptosis.

Mechanical irritation of the intestine produces peristalsis above and relaxation below; the distension with fæces which occurs above an obstruction acts as such an irritant. An attempt is thus made to overcome the obstruction by increased peristalsis, and the intestinal contents generally travel with abnormal rapidity as far as the obstruction. In chronic organic obstruction the over-activity of the proximal part of the intestine leads to hypertrophy of its musculature. When at last the hypertrophied muscle fails to overcome the increasing obstruction, extreme paralytic distension occurs, and the muscle finally ceases to respond to any kind of stimulus.

The increased motor activity above the seat of obstruction does not manifest itself as purposive peristalsis only. Violent spasmodic contractions of various lengths of intestine occur, which lead to "stiffening" of the intestine, the contracted gut forming a palpable and often visible tumour.

The stimulus to increased motor activity above the seat of obstruction is not due to distension alone, as the fluid present in

the intestine above the obstruction contains a substance which acts as a powerful stimulant to its contraction.

When the cæcum is greatly distended as a result of obstruction of the colon, the ileo-cæcal sphincter becomes incompetent, just as in dilatation of either ventricle of the heart the auriculo-ventricular valve becomes incompetent and regurgitation results. When such incompetence of the ileo-cæcal sphincter occurs, the rapid retrograde movement produced by the "stiffening" of the colon may extend to the small intestine and give rise to fæcal vomiting.

The relaxation, which occurs below an irritated part of the intestine, is probably the cause of the "ballooned" rectum often found in cases of obstruction of the lower part of the colon.

### 2. Dyschezia.

In dyschezia, the second of the three great classes of constipation, the passage of fæces through the intestines is normal or unusually rapid, but the act of defæcation does not empty the part

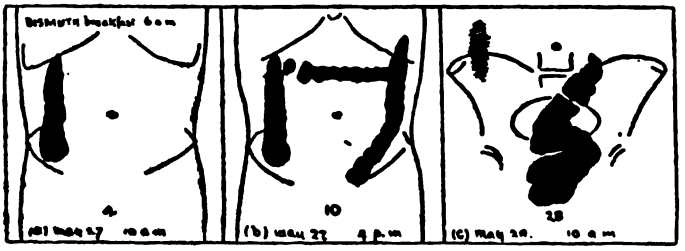


FIG. 38.—DYSCHEZIA DUE TO LAZINESS IN A GIRL OF SIXTEEN YEARS OF AGE.

of the bowel beyond the splenic flexure as completely as it should. Hence although the bowels may be opened daily, the fæces become unduly hard owing to excessive absorption of water during their long retention in the rectum and pelvic colon, or cumulative constipation results from the slight daily deficiency in the quantity of fæces excreted compared with the quantity produced. In severe cases defæcation is not only incomplete, but it does not occur daily, and finally it may become quite impossible to defæcate without mechanical assistance.

Dyschezia differs from other forms of constipation in that considerable quantities of fæces are found in the rectum whenever an examination is made, even immediately after defæcation. The only exception to this is in the dyschezia which is due to inability to pass the contents of the pelvic colon into the rectum, the evacuation of which, when once it is filled, offering no difficulty.

Dyschezia is due to a want of proper proportion between the power of expelling the fæces from the pelvic colon and rectum and the force required to do this completely. It may therefore be

due to (1) inefficient defæcation or (2) an obstacle to efficient defæcation.

(1) *Dyschezia due to Inefficient Defæcation.*—This is most frequently due to habitual disregard of the call to defæcation, either on account of ignorance or laziness (Fig. 38), or of fear of pain in diseases of the anus and neighbouring organs. I have already described how the sensation of fulness in the rectum passes off, owing to relaxation of the tonic contraction of its muscular coat, if the call to defæcation is disregarded. If it is again disregarded after its return on the arrival of more fæces in the rectum, further relaxation occurs. More and more fæces accumulate in the rectum, the muscular coat of which becomes more and more relaxed. As the force required to empty the rectum when overdistended with fæces is much greater than that required to empty it under normal conditions, evacuation is now likely to be incomplete, even if a great effort be made. Consequently fæces are always present in the rectum instead of only for a few minutes before defæcation, and

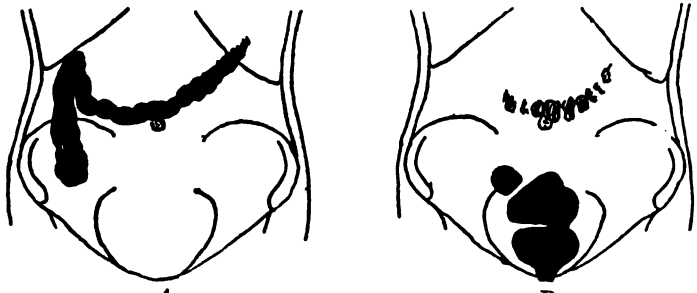



FIG. 39.—CONGENITAL DYSCHEZIA.

*A*, Ten hours after a bismuth meal; *B*, thirty-four hours after a bismuth meal. Rectum distended with fæces, but there was no desire to defæcate.

the lumen of the rectum is permanently increased owing to the atony of its muscular coat.

This form of dyschezia may also result from the incomplete evacuation, which is caused by weakness of the voluntary muscles of defæcation, and by the assumption of an unsuitable position during defæcation. But whatever the primary cause, the final result is the same. The incomplete evacuation of the rectum results in an accumulation of fæces and in its atonic dilatation.

As the rectal mucous membrane is normally insensitive to touch, the absence in dyschezia of any sensation when the rectum is full of fæces cannot be due to a blunting of the sensibility of the mucous membrane. In most cases the intrarectal pressure required to produce the call to defæcation is not greater than normal, the dyschezia depending upon the atonic dilatation of the rectum; an abnormally large quantity of fæces is required to exert the normal adequate pressure. In extreme cases a blunting of the

muscle sense may also occur; the rapid and considerable d produced by an enema then fails to produce the artificia defæcation, which in most cases of dyschezia results in a m of the bowels.

There is, however, an entirely distinct class of dyschez depends upon deficiency of the muscle sense of the rectum genital deficiency causes the dyschezia, which occurs commonly in infants, in whom the slight additional di produced by the introduction of a finger or a piece of soap rectum results in an adequate stimulus (Fig. 39). In the maj cases the muscle sense develops when the infant grows old occasionally this may be the starting-point of dyschezia

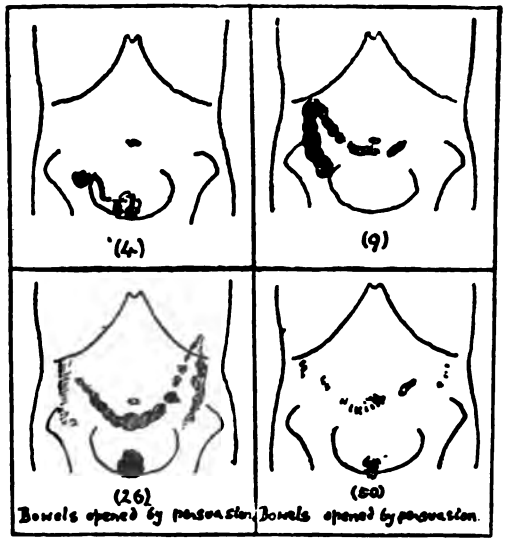



FIG. 40.—HYSTERICAL DYSCHEZIA, CURED BY PERSUASION.

lasts through life. The rectal muscle sense is abolished or defec in diseases of the spinal cord, in which the defæcation centre it or the fibres connecting it with the brain are involved. This is cause of the constipation, which so frequently occurs in orga nervous diseases, the passage through the intestines remain unaffected.

Just as retention of urine may occur in hysteria as a res of auto-suggestion, so dyschezia may result if a patient sugge to himself that he cannot open his bowels. In a milder and mo frequent form of hysterical dyschezia, the patient persuades hi self that he is quite unable to defæcate unless he takes a purgati or an enema, although in reality no such artificial help is require The dyschezia produced by suggestion is, like hysterical paralys

and anæsthesia, a genuine thing, the patient being quite unable to open his bowels, however much he tries. But hysterical dyschezia, like hysterical paralysis and anæsthesia, is always curable by suggestion and persuasion alone. If such a patient can be persuaded, after a thorough examination, that there is really no reason why he should not obtain a daily action of his bowels, he will have no difficulty in curing himself (Fig. 40).

(2) *Dyschezia due to Obstacles to Defæcation.*—Efficient defæcation may be prevented by abnormally hard and bulky fæces, and by obstruction of the rectum and anal canal. The latter may result from spasm of the anal sphincters, organic stricture of the rectum or anus, an abnormal degree of kinking at the pelvi-rectal flexure, and pressure on the rectum from without.

### 3. Insufficient Formation of Fæces—"Greedy Colon."

In addition to the two great classes of constipation already considered there is a third, in which the quantity of fæces formed is insufficient to produce an adequate stimulus in the pelvic colon and rectum and to a less extent in the proximal part of the large intestine. The passage through the small intestines in such cases is always normal; that through the colon is generally slightly delayed, but the main stasis is in the pelvic colon and occasionally in the rectum, as it may take several days before a sufficient bulk of fæces has collected to produce an adequate call to defæcation. The insufficient bulk of fæces is due to too little food residue reaching the colon, as a result of anorexia or œsophageal or pyloric obstruction, or to excessive digestion of food. The total weight of fæces voided by constipated individuals is considerably less than that passed by normal people. This is due not merely to the greater dryness of constipated stools, but also to a diminution in the solid constituents of the fæces. A remarkably small quantity of food débris, such as muscle fibres, starch cells and vegetable membranes, is found in constipated stools, and the amount of nitrogen, fat and cellulose, as well as the number of bacteria, in the fæces is considerably less in constipated than in normal individuals. The diminution in water is simply due to increased absorption, owing to the abnormally long period during which the intestinal contents are retained before excretion. In most cases this is also the cause of the diminished quantity of food residue and intestinal secretion, as both of these are likely to be absorbed during their prolonged retention in the colon. Sometimes, however, a diminution in the quantity of fæces is due to an abnormally active digestion in the intestines, a condition which Goodhart has called *greedy colon.* This results in a deficiency in the culture media required for the growth of bacteria in the large intestine, as shown by the diminution in the number of bacteria in the stools; for this reason

there is less production by putrefaction and fermentation of substances which normally act as stimulants to the intestinal movements.

### C. Diarrhœa.

Diarrhœa is a condition in which fluid stools are passed. Defæcation generally occurs several times in the day, but mere frequency of defæcation is not diarrhœa, for this may even occur with constipation. The essential factor in diarrhœa is the abnormally rapid passage of the food residue through the alimentary canal; diarrhœa is therefore the direct counterpart of intestinal constipation. The fæces are fluid when they reach the cæcum and only become solid in the distal part of the transverse colon. Consequently excessive rapidity in the passage of fæces through the small intestine only results in diarrhœa, if the passage through the colon is also abnormally rapid. On the other hand, diarrhœa may result from the latter without any increase in the rapidity with which the cæcum is reached. Thus small doses of castor-oil may increase the peristalsis of the small intestine without causing diarrhœa, whereas severe diarrhœa may result from ulcerative colitis, although the fæces pass through the healthy small intestine at the normal rate.

The abnormally rapid passage of fæces through the colon gives rise to diarrhœa, as it allows insufficient time for fluid to be absorbed. In some cases, however, deficient absorption, and in others excessive secretion, is the primary cause of the diarrhœa, the rapid passage through the colon being due to the distension produced by the excessive bulk of the intestinal contents acting as a stimulus to its muscular activity. Hence the causes of diarrhœa may be divided into three groups, in which the chief factor is (1) excessive motor activity, (2) deficient absorption, and (3) excessive secretion. The classification is not a rigid one, as excessive stimulation of motor activity always results in deficient absorption, and the mechanical and chemical irritants, which give rise to increased motor activity, often simultaneously excite excessive secretion; moreover, both deficient absorption and excessive secretion give rise to excessive motor activity.

1. **Excessive Motor Activity.**—Excessive motor activity may be due to (*a*) excessive stimulation or (*b*) excessive excitability of the neuro-muscular mechanism which controls the intestinal movements.

(*a*) *Excessive Stimulation of Motor Activity.*—Certain emotions, such as excitement and pleasure, especially in neurotic individuals, can lead to diarrhœa, the stimulus to increased intestinal activity being probably conveyed by the vagus to the small intestine and by the pelvic nerves to the colon. Diarrhœa frequently results from the presence in the food of excess of the mechanical and chemical stimulants of intestinal activity. Excess of cellulose, such as occurs

in the diet of vegetarians, always leads to increased motor activity of the intestines, which is, however, partly due to the large quantity of chemical stimulants present in vegetable food. The commonest cause of diarrhœa is excessive chemical stimulation of the intestines. This may result from the taking of purgatives or the excessive consumption of vegetables and fruit containing organic acids and their salts and sugar, all of which stimulate peristalsis to a greater or less extent. Chemical irritants may also be introduced in decomposing food, and a further quantity may be produced in the alimentary canal by the micro-organisms in the food.

Excessive fermentation of carbohydrates, which occurs in fermentative intestinal dyspepsia, may lead to diarrhœa, as the organic acids and carbon dioxide produced are powerful stimulants to peristalsis. The sulphuretted hydrogen and probably some of the amido-acids and other substances, which result from the putrefaction of proteins, also stimulate intestinal movements, so that excessive putrefaction in the colon is generally accompanied by diarrhœa. Under normal conditions very little protein reaches the colon, and putrefaction only occurs to a limited extent. In inflammatory conditions of the intestine, however, there is an excessive secretion of fluid containing protein; this provides material for the action of putrefactive organisms, which at the same time increase in number, as the intestinal contents act as a favourable culture medium for them. The structural changes in the mucous membrane are not so much a cause of the diarrhœa as a result, like the diarrhœa, of excessive irritation by the products of abnormal decomposition.

Diarrhœa is sometimes gastric in origin. This *gastrogenous diarrhœa* occurs whenever the gastric juice is deficient or absent. An abnormal number of organisms under these circumstances reaches the intestines, as the partial protection afforded by the bactericidal action of the hydrochloric acid in the stomach is lost. Moreover, when the quantity of gastric juice is deficient, the connective tissue of meat is insufficiently softened. Consequently protein and fat are less accessible to the digestive juices in the small intestine and may reach the colon in excess, where they are liable to undergo bacterial decomposition and so give rise to diarrhœa. The undigested masses of meat also act as mechanical stimulants to peristalsis.

Lastly, chemical stimulants to intestinal activity may be produced in the body and excreted into the colon, as in uræmia, Graves' disease and septicæmia.

(*b*) *Overexcitability of the Neuro-Muscular Mechanism which controls Intestinal Movements.*—When the mucous membrane of the colon is acutely inflamed or ulcerated, any mechanical or chemical stimulant is likely to produce an excessive reflex response, so that the tendency to diarrhœa in such cases is increased. In irritable

conditions of the central nervous system a stimulus, which produces only a slight effect under normal circumstances, may give rise to diarrhœa. Thus the taking of food reflexly stimulates intestinal activity, and in some neurotic individuals the effect is so much exaggerated that a liquid stool is passed immediately after each meal, the condition known as *lienteric diarrhœa* resulting.

2. **Deficient Absorption.**—Just as constipation may result from excessive digestion of food, so diarrhœa is occasionally due to a congenital or acquired deficiency in the absorptive power of the colon. This condition gives rise to the passage of excessive quantities of fæces, defæcation occurring with abnormal frequency; but the stools are not necessarily fluid, and the rate of passage through the intestines may be normal, so that the majority of these cases cannot be correctly described as diarrhœa.

Deficient absorption is more frequently due to organic disease of the colon. In acute colitis, especially when it is associated with ulceration, and in lardaceous disease, absorption is very deficient; this is an important factor in the diarrhœa which generally accompanies these conditions. When ulceration is confined to the small intestine, or, as in typhoid fever, to the lower end of the small intestine and the cæcum and ascending colon, diarrhœa is frequently absent, as the absorption in the distal part of the colon may be unaffected. When, as in dysentery and in most cases of sporadic ulcerative colitis, the ulceration involves the distal part of the colon, where the fæces are normally solid, diarrhœa generally results.

Deficient absorption in the colon leads merely to an increase in the quantity of water in the fæces, as normally almost all the products of digestion of the food are absorbed in the small intestine.

When, however, there is deficient absorption in the small intestine, excess of protein, carbohydrate and fat reach the cæcum. Consequently diarrhœa affecting the colon alone does not necessarily interfere with nutrition; but when the small intestine is also affected, a considerable amount of protein, fat and carbohydrate may be lost in the fæces. In the latter condition there is consequently an excessive supply of material for bacterial decomposition, the products of which are likely to irritate the colon and lead to diarrhœa, even in those cases in which the colon is not affected simultaneously with the small intestine by the primary disease.

3. **Excessive Secretion.**—Many of the substances which stimulate the movements of the intestines also stimulate the secretion of intestinal juice. Excessive secretion is therefore often a factor in the diarrhœa, which results from the presence in the colon of excess of the chemical stimulants already described. It is impossible to determine in any given case whether the diarrhœa produced by an irritant is more a result of excessive motor or excessive secretory activity. Vegetable purgatives probably stimu-

late peristalsis more than secretion, but saline purgatives stimulate secretion more than peristalsis.

The excess of fluid derived from the mucous membrane is not always intestinal juice. Irritation of the mucous membrane generally results also in excessive secretion of mucus; in severer cases inflammation and ulceration result, and a serous exudation is produced.

## VI. THE PANCREATIC JUICE.

The pancreatic juice contains proteolytic, amylolytic, lipolytic and milk-curdling enzymes. Its alkaline reaction also helps to neutralize the acid chyme and to emulsify fats and form soaps from the fatty acids produced by its lipolytic ferment.

The sight, smell and taste of food produce an almost immediate flow of pancreatic juice, the efferent impulse being carried by the vagus. A few minutes later the psychical secretion of gastric juice begins, and acid chyme enters the duodenum. This sets up a further flow, as hydrochloric acid is the most important stimulant to pancreatic secretion. The hydrochloric acid acts by converting the prosecretin present in the duodenal mucous membrane into secretin, which passes into the circulation and stimulates the secretory activity of the pancreas. The sodium bicarbonate of the pancreatic juice and bile is more than sufficient to neutralize the hydrochloric acid of the chyme, so that the pancreatic ferments, which are destroyed by acid, can act upon any food which has escaped digestion in the stomach.

As fat inhibits the flow of gastric juice, and as its digestion largely depends upon the steapsin of pancreatic juice, it would remain undigested if hydrochloric acid were the only chemical stimulant of pancreatic secretion. It is, therefore, not surprising that the presence of both fat and soap in the duodenum stimulate the secretion of pancreatic juice. The former appears to act reflexly, but the latter acts by giving rise to a special secretin. Water and the products of protein digestion also act as stimulants to pancreatic secretion, but carbohydrates, raw proteins, meat extracts and neutral salts have no action, and alkalies inhibit it.

**Pathological Variations in the Secretion of Pancreatic Juice.**—As hydrochloric acid is the most important stimulant to the secretion of pancreatic juice, variations in the secretion of the former have an important influence on intestinal digestion. Hypersecretion of gastric juice leads to hypersecretion of pancreatic juice. This results in the complete neutralization of the excess of hydrochloric acid in the second part of the duodenum, and protects the intestine from the ulceration, which might otherwise result from the action of the acid.

Deficient secretion of hydrochloric acid leads to deficient secretion

of pancreatic juice. Hence the insufficient digestion of protein in the stomach is not compensated for by increased proteolytic activity in the intestine. In spite of this, digestion and absorption may be quite normal in achylia gastrica and after gastro-enterostomy, if care is taken to chew the food thoroughly and to eat slowly. Under these conditions the psychical secretion of pancreatic juice is of special importance, and the presence of fat in the food is a valuable aid to digestion on account of its stimulating action on pancreatic secretion. Deficient secretion of pancreatic juice also occurs in chronic pancreatitis and cancer of the pancreas, and in obstruction of the pancreatic and common bile ducts by growths and by biliary and pancreatic calculi.

**Results of Deficient Pancreatic Digestion.**—Any carbohydrates, which are not digested in the mouth or stomach by the saliva, can be completely digested by the ferments of the intestinal juice in the absence of pancreatic juice. But there is nothing which can take the place of trypsin and steapsin, so that when no pancreatic juice reaches the intestine the digestion of proteins and fats is deficient, and excess of nitrogen and undigested muscle fibres, together with excess of fat, is present in the fæces. Nucleins are unaffected by any digestive secretion except the pancreatic juice; the presence of nuclei in the stools alone or in muscle fibres is therefore a characteristic feature of pancreatic insufficiency. Rather more fat is present in the fæces in the absence of pancreatic juice than in the absence of bile, and owing to the loss of the lipolytic action of steapsin most of the fat is unsaponified, and numerous fat droplets and comparatively few crystals of calcium soap are present in the fæces. When, however, the pancreatic disease is complicated by colitis, in which excessive bacterial decomposition is likely to occur, very active saponification may take place in the large intestine, and the fæces may contain more soap and fatty acid than neutral fat. If fats are supplied as emulsions, they are to some extent split up by the lipolytic ferment of the stomach; consequently emulsified fats are better absorbed than non-emulsified fats in the absence of pancreatic juice.

Pancreatic juice is neither an antiseptic nor a stimulant to peristalsis. But the insufficient digestion of protein in the absence of pancreatic juice results in a great increase in putrefaction, owing to the large quantity of undigested protein which reaches the colon. Many of the products of putrefaction stimulate peristalsis and irritate the intestinal mucous membrane, so that diarrhœa and colitis are likely to result.

Owing to the anatomical connections between the bile and pancreatic ducts, deficient pancreatic secretion is frequently associated with deficiency of bile. The steatorrhœa which results is due to both, but the azotorrhœa is due to the pancreatic insufficiency alone.

## VII. THE BILE.

Although bile is constantly secreted by the liver, it only enters the duodenum when food is present. In the intervals it passes along the hepatic and cystic ducts into the gall-bladder, where it is stored until required. Its flow into the duodenum begins about half an hour after a meal and continues as long as chyme leaves the stomach. The chief stimulants to the discharge of bile into the intestine are fat, the extractives of meat and the products of protein digestion; mechanical stimulation, water, undigested proteins and hydrochloric acid have no such effect.

On the other hand, the chief stimulant to the secretion of bile by the liver is hydrochloric acid, which acts in the same way as it does in the case of pancreatic juice—by means of secretin. Consequently the secretion of bile is diminished when there is a deficient secretion of hydrochloric acid in the stomach, and gastric hypersecretion is associated with an increased secretion of bile, which helps the pancreatic and intestinal juices to neutralize the abnormally acid chyme.

The secretion of bile is also slightly increased by the presence of hæmoglobin in the blood, and the proportion of pigment in the bile is augmented. Hence hæmolytic poisons give rise to the secretion of an increased quantity of abnormally thick bile.

The most important function of bile is to increase the activity of the pancreatic ferments. But although the proteolytic and amylolytic action of pancreatic juice is doubled by its admixture with bile, the absorption of proteins and carbohydrates is unaffected by the absence of bile. Not only does bile increase the lipolytic action of steapsin, but it also dissolves and increases the solubility of soaps, and so renders their absorption more easy. Consequently, when bile is absent from the intestines, but pancreatic juice is still secreted, from a quarter to a half of the fat taken in the food is unabsorbed. Hence the fæces are very bulky and may float on water. The proportion of soap and fatty acid to neutral fat is not affected, as the fat-splitting action of bacteria and of the lipase of the intestinal juice compensates for the loss of the stimulating effect of bile on the activity of steapsin. The large quantity of fatty acid present in the fæces causes them to be very acid, and numerous crystals of calcium soap can be recognized. The emulsifying power of bile is of no great importance, as the proportion of fat absorbed in biliary obstruction is not increased by supplying it in an emulsified condition.

Bile is not, as has sometimes been supposed, an antiseptic; consequently the absence of bile from the intestinal contents neither increases the number of bacteria nor their fermentative or putrefactive activity.

Although bile acts as a mild stimulant to peristalsis in the colon, the bowels often remain perfectly regular in patients with severe obstructive jaundice; this is due to the presence in the colon of excess of fatty acid, soaps and fat, all of which stimulate intestinal movements.

## VIII. INTESTINAL SECRETION.

### A. Intestinal Juice.

Mechanical stimulation of the small intestine leads to the secretion of a juice which contains very little ferment. Its function is to wash away the irritant, and the diarrhœa which results from excessive mechanical irritation of the bowels is doubtless a result of the secretion of this watery intestinal juice.

The chief stimulant to the secretion by the small intestine of its normal ferment-containing juice is pancreatic juice, the action of which is local and dependent upon its ferments, as it is destroyed by heat. The presence of hydrochloric acid, fat and soap in the duodenum causes a secretion of juice by the duodenal, and to a less extent by the jejunal, mucous membrane; this is due to the production of secretin. Consequently the flow of intestinal juice, as well as that of pancreatic juice and bile, is diminished when the secretion of hydrochloric acid is deficient.

The absorption of the juice secreted by one part of the intestine is said to stimulate the secretion of juice by the part of the intestine immediately below.

The secretion of the colon, which contains a small quantity of ferments similar to those present in the secretion of the small intestine, depends more upon mechanical stimulation by its contents than upon their chemical constitution.

Variations in the quantity of intestinal juice are exceedingly difficult to recognize, but they are probably of more importance in intestinal pathology than has generally been supposed. The intestinal juice contains invertin, which splits cane-sugar, maltase, lactase and a cellulose-splitting ferment, but not one with an amylolytic action. In the condition known as *intestinal flatulent dyspepsia* the digestion of cellulose is defective, even the tender capsule of potato cells being undissolved, whereas cellulose-free starch and sugars are well digested. As the cellulose capsules of vegetable cells are undigested, excess of starch reaches the colon and supplies nutriment for fermentative organisms, with the result that excessive fermentation occurs. The stools are bulky and frothy; they contain excess of carbohydrates, and fermentation continues in them if they are incubated.

Intestinal juice contains two ferments, enterokinase and erepsin, which play an important part in the digestion of proteins, enterokinase by activating trypsinogen, and erepsin by splitting albumins

and peptones into simpler crystalline bodies. Consequently a slight excess of nitrogen is present in the stools in some cases of intestinal fermentative dyspepsia. The digestion of fat is unaffected, as steapsin can normally split all the fat that the food contains without the aid of the intestinal lipase.

### B. Intestinal Mucus.

A small quantity of mucus is normally secreted by the intestinal mucous membrane. It becomes so intimately mixed with the other contents of the bowel that it cannot be recognized in the fæces except by special chemical methods. Mechanical and chemical irritation acts upon the intestinal mucous membrane in the same way as upon the gastric mucous membrane, an excess of mucus being produced. If the irritation is strong or long-continued, catarrh with overgrowth of the mucin-producing epithelial cells results, an excess of mucus being then constantly secreted, even after the disappearance of the irritant which produced the catarrh.

Stimulation of the vagus causes an increased secretion of mucus in the rabbit's intestines. It is probable, therefore, that irritants may act reflexly as well as directly on the mucin-secreting cells. This is particularly likely to occur if the nervous system is abnormally excitable. Consequently, in neurasthenic individuals retention of fæces may cause reflex activity of the motor and secretory fibres of the colon, leading respectively to painful spasm and excessive secretion of mucus. The intestinal mucous membrane secretes a ferment, mucinase, which is capable of coagulating mucin in about ten hours, the change being analogous to that which occurs when fibrinogen is converted into fibrin. The spasm, which generally accompanies the reflex secretion of mucus, leads to delay in its evacuation; there is thus sufficient time for coagulation to occur, and consequently a membrane formed of coagulated mucus is produced. This is the pathology of the condition known as *muco-membranous colitis*, which occurs frequently in individuals, who are at the same time both neurasthenic and constipated.

## IX. BACTERIAL ACTIVITY IN THE ALIMENTARY CANAL.

Most of the organisms, which are normally present in the alimentary canal and which under certain conditions lead to excessive fermentation and putrefaction, enter the body in the food and in water. They consequently vary considerably in number according to the diet and the time of the year, uncooked fruit and vegetables being the most prolific source of living bacteria. Pathogenic organisms, which are normally absent from the alimentary canal, may also be introduced in the food and drink, or they may be derived from

septic foci in the mouth, as in pyorrhœa alveolaris, or be swallowed with the secretions in infective conditions of the pharynx, accessory nasal sinuses and bronchi.

A. **The Stomach.**—Of the enormous number of bacteria, which are daily introduced into the stomach, only a small proportion remain undestroyed by the hydrochloric acid and pass into the intestine. Under normal conditions the activity of the bacteria, which are not destroyed by the acid, seems to be inhibited by it, as fermentation does not occur in the stomach except when an excessive quantity of food is taken, and the occurrence of putrefaction of proteins is always pathological.

Fermentation and putrefaction may occur in the stomach, when the quantity of hydrochloric acid present is deficient and when the evacuation of the stomach is abnormally slow, but the latter is of much greater importance than the former. Well-marked gastric hypersecretion does not prevent fermentation from occurring in the stomach if stasis is present; thus the continuous hypersecretion which occurs when an ulcer is situated at the pylorus, is associated with excessive fermentation, as the passage of food into the duodenum is simultaneously delayed. In pyloric obstruction due to cancer free hydrochloric acid is generally absent and active hydrochloric acid is much diminished, and at the same time there is a considerable degree of stasis. The excessive bacterial decomposition, which invariably occurs, diminishes and often entirely disappears after gastro-enterostomy, although this only relieves the stasis without influencing the secretion of hydrochloric acid.

The only organisms, which can flourish in the stomach when the secretion of the hydrochloric acid is normal or excessive, are those which give rise to alcoholic fermentation, by which cane-sugar, lactose and dextrose are broken up, and alcohol, which may further undergo acetic acid fermentation, and carbon dioxide, are produced. When hydrochloric acid is deficient, lactic acid fermentation is more prominent, lactose being decomposed and lactic acid, carbon dioxide and hydrogen produced. The lactic acid may undergo further decomposition, butyric acid and a further quantity of carbon dioxide and hydrogen resulting. Small quantities of acetic and formic acids and of marsh gas may also be formed. The organic acids produced by fermentation irritate the gastric mucous membrane and may give rise to gastritis.

Putrefaction only occurs in the stomach in severe cases of combined motor and secretory insufficiency, except for a short period in the acute indigestion, which may follow the rapid consumption of a large and indigestible meal. It never occurs to any considerable extent, as both hydrochloric acid and lactic acid inhibit the development of putrefactive bacteria. Sulphuretted hydrogen and ammonia are produced, but the other products of putrefaction, such as tyrosin and phenol, have never been found in the stomach.

B. **The Intestines.**—Fermentation normally occurs in the lowest part of the ileum and in the colon, but putrefaction only occurs in the colon. Both forms of bacterial activity are more active in the cæcum and ascending colon, the contents of which are semi-fluid, than in the distal parts of the colon, in which the fæces are more or less solid. The number of active bacteria also diminishes as the fæces become drier, a large proportion of the bacteria in normal stools being dead.

The products of bacterial decomposition in the intestine only appear in small quantities in the fæces and flatus. The greater part is absorbed, the carbon dioxide being exhaled by the lungs, and the organic acids and bases being oxidized in the blood or excreted in the urine, unaltered, as ethereal sulphates, or combined with glycuronic acid.

The influence of deficient secretion of gastric juice, bile and intestinal juice on intestinal bacterial activity has already been discussed.

The moderate degree of intestinal stasis which occurs in constipation is not associated with increased decomposition; it has, indeed, been found that in most cases of constipation the number of bacteria in the stools and the amount of putrefaction in the alimentary canal are diminished. In intestinal obstruction, however, stasis of fluid fæces occurs, the conditions being thus favourable for bacterial activity. A large quantity of gas develops and leads to the characteristic abdominal distension present in such cases, and the absorption of other products of bacterial decomposition leads to severe auto-intoxication.

The influence of diet on bacterial decomposition is considerable, the amount of fermentation depending on the quantity of carbohydrates in the food, and that of putrefaction on the quantity of protein. This is of more importance in the stomach than in the intestine, as very little undigested food normally reaches the colon, which is the only part of the bowel in which large numbers of bacteria are present. But if for any reason digestion in the small intestine is deficient, the increased quantity of protein or carbohydrate which reaches the colon leads to an increase in putrefaction or fermentation.

## X. THE GASES OF THE ALIMENTARY CANAL.

Under normal conditions the amount of gas, which is produced in and introduced into the alimentary canal, is equal to the amount which is eliminated, so that the quantity actually present remains constant. The gases of the stomach and intestines are derived for the most part from bacterial decomposition and from air swallowed with the food. It has already been explained that fermentation of carbo-

hydrates only occurs in the healthy stomach when an excessive quantity of food is taken, and that putrefaction of proteins in the stomach is always pathological. On the other hand, a certain amount of bacterial decomposition of both carbohydrates and proteins normally occurs in the intestines, particularly in the colon, and consequently a considerable proportion of the gas in the bowels results from bacterial activity. Every time a mouthful of food or fluid is swallowed a certain amount of air is swallowed with it. This occurs not only at meals, but also whenever saliva is swallowed. A small quantity of carbon dioxide is normally produced by the action of the hydrochloric acid of the gastric juice on the alkaline carbonates of the food and saliva. This occurs more particularly with vegetable foods, because they contain a greater quantity of alkaline carbonates than animal foods. It has been supposed that gas may diffuse from the gastric and intestinal mucous membrane, but in all probability this never really occurs.

A large proportion of the gas eliminated from the alimentary canal is absorbed by the mucous membrane. Oxygen is taken up with great rapidity, so that although a considerable amount is swallowed with the air, under normal conditions none is present in the large intestine, as it is all absorbed in the stomach and to a less extent in the small intestine. Enormous quantities of other gases can be absorbed under special circumstances. This is well seen in the rapid absorption of carbon dioxide after large quantities of aerated drinks have been consumed, when excess of gas is not necessarily expelled either by the mouth or the rectum.

No gas is expelled by eructation under normal conditions, but a varying quantity is expelled from the rectum as flatus. Eructation, however, serves as an additional means of elimination, whenever excess of gas is present in the stomach.

**Flatulence.**—Flatulence, or the presence of excess of gas in the alimentary canal, may be due to excessive production and introduction of gas and to deficient elimination of gas. The former may be due to excessive bacterial activity, the causes of which have already been described, and to aerophagy.

*Aerophagy* is the commonest cause of flatulence. In most cases it is associated with nervous dyspepsia, but it may also occur in organic diseases, such as gastric and duodenal ulcer. The patient feels some slight discomfort in the stomach, which he thinks must be due to "wind," and which he imagines he can "disperse" by means of eructation. But the attempt to eructate is unsuccessful, as there is really no excess of gas present in the stomach, and the unsuccessful attempt results in the swallowing of air. Often half a dozen or more attempts are made without success, air being swallowed at each attempt. The stomach becomes so distended with gas that an attempt is at last successful, the gas expelled being odourless, because it is nothing but air. Salivation is another

common cause of flatulence, as every time saliva is swallowed some air is swallowed with it.

Deficient absorption of gas probably occurs in catarrh of the stomach and intestines. Absorption is greatly diminished when the venous circulation is obstructed, and ceases entirely when the latter is completely arrested. This is the cause of the extremely rapid distension, which occurs when part of the bowel is strangulated, as in intestinal obstruction. The gas is produced entirely by fermentation and does not diffuse from the blood-vessels into the intestine, as ligature of the veins of an isolated piece of bowel does not result in distension if the latter has previously been washed out.

Deficient expulsion of gas, except in association with constipation, is not of great importance. Pyloric obstruction prevents the rapid passage of gas as well as of fluids into the duodenum, so that the gas, which is likely to be produced in excess in such cases, tends to accumulate in the stomach. Constipation does not lead to excessive decomposition, but the colon may contract so firmly upon fæces moving along it with abnormal slowness that the gas which is behind cannot pass; consequently retention of gas occurs in addition to retention of fæces.

## REFERENCES.

Numerous references to the subject are given in the following work:

*Hertz:* Constipation and Allied Intestinal Disorders, 1909.

## CHAPTER XIV

# METABOLISM

By M. S. PEMBREY

**Introduction.**—The living body was considered by the early physiologists as the unit, but in time this logical view was displaced by undue consideration of the various organs of which the body is compounded. The organs were found to be composed of tissues and the tissues of cells, and the search for the final unit of life did not end there. Altmann,* a few years ago, proclaimed the view that the cell is a collection of living granules, comparable in some measure to bacteria aggregated together to form a zooglea; and quite recently Macallum,† in an interesting discussion on the origin of life, has suggested that the units of life are ultramicroscopic particles.

The application of the cellular theory to physiology and pathology has produced great advances in many directions, but too much has been claimed for the conception and method. It has not been possible to construct the physiology or pathology of an animal from a study of its component cells. The attempt has failed, as did the earlier one based upon the investigation of the separate organs of the animal. The numerous observations upon masses of dying cells in so-called "surviving" organs have yielded interesting results, but these results do not represent a true picture of the parts played by the organs in the living body. The isolated organ is no longer influenced by other organs; it is in a purely artificial condition, which never occurs in a state of health or disease. There is a constant interchange of material between the different parts of the living organism. This complex exchange is one of the most characteristic signs of life; there is an intake and building up, and a breaking down and output of waste material. The former process is known as *anabolism*, or *assimilation*, the latter as *katabolism*, or *dissimilation*, and the total exchange is represented by the term *metabolism*. The unorganized products of the activities of the cells are called *metabolites*.

The exchange of material in the higher forms of life is not limited

* *Die Elementarorganismen*, Leipzig, 1894.

† Transactions of Canadian Institute, vol. viii., p. 423.

to the taking up of food by the alimentary canal, the absorption of oxygen by the lungs, and the discharge of waste products by the bowel, kidneys, skin, and lungs. There is an exchange between the different organs, and for the welfare of the animal as a whole this internal exchange is essential. The ductless glands, for example, produce internal secretions, which in varying degrees are necessary for the due sequence of the chemical changes in metabolism. There is a wide range in the power of man to adapt himself to qualitative and quantitative changes in his food, but diminished or increased activity of his ductless glands may not be compensated readily, and may be associated with well recognized disorders. Pathological conditions of metabolism have their representation in physiological processes. For this reason disorders of nutrition can be studied best by comparative observations and experiments.

Some of these problems of nutrition are so large that they have been discussed in special articles.* There remain some general questions of nutrition, which will now be considered under—(1) External exchange, and (2) internal exchange. The first group is concerned chiefly with diet, the second with the so-called "internal secretions."

## EXTERNAL EXCHANGE.

**The Quantity and Quality of the Food required by Man.**—The great differences in the nature of the food of man is shown by a comparison of the dietaries of different races. Some are vegetarians, others live upon a mixed animal and vegetable diet, and others upon an animal diet. These variations appear to have been determined by the nature of the climate of the country and its products. In warm climates cereals, vegetables, and fruits will grow so readily that the inhabitants have at hand an easy source of sustenance; moreover, owing to the external warmth, concentrated food is not necessary for the production of heat to maintain the temperature of the body. In colder climates, on the other hand, vegetation is restricted, and, although grass will grow all the year round, man has not been able to utilize it as food for himself. Cattle feed on the grass, and man in turn feeds on them.

It is impossible to dogmatize upon the question of diet. The fact that the most energetic races at the present time eat a large quantity of meat does not justify the conclusion that such a diet is the best for all. It is more probable that the energy of these races is the response to the climatic conditions under which they

* "The Physiology and Pathology of Digestion," by Dr. Hertz; "Respiration," by Dr. Haldane; "The Metabolic Disturbances which Result from Hepatic Disease," by Dr. Garrod; "Anomalies of Metabolism," by Dr. Garrod; "Diabetes Mellitus and some Other Changes in Carbohydrate Metabolism," by Dr. Beddard; "Gout," by Dr. Walker Hall; and "Fever," by Dr. Pembrey.

have developed. The variable and uncertain climate of a country such as England introduces in the struggle for existence the necessity of adaptation. The demand for food, clothing, and shelter, becomes the chief stimulus to commerce and all the activities with which it is associated. On the other hand, the extreme view of vegetarians that vegetable food is the best for temperate climates is not supported by evidence. Many so-called "vegetarians" take milk and eggs, which are the two animal foodstuffs which contain all the necessary components of a diet. Upon milk alone all young mammals live during the early months of life, when their growth is most active, and it matters not whether in later life they will become herbivorous, carnivorous, or omnivorous. The egg is a perfect food, for the chick finds in it all that is necessary for its development and growth during the twenty-one days of incubation. Men who eat eggs and drink milk are not vegetarians. Most vegetable substances are not concentrated foods, and to obtain from such a source a given supply of nitrogenous material and energy, a herbivorous mammal requires to eat more than does a carnivorous or omnivorous mammal. Herbivorous animals are characterized by the large size of their alimentary canal and their frequent need of food. Other arguments have been brought forward in support of a vegetarian diet. One of these is that it is not liable to cause disease. It is known, however, that beri-beri and polyneuritis are produced in man and animals by a diet consisting too largely of polished rice, and ergotism and pellagra are due to unsound corn.*

Whatever may be the nature of the diet, the food of man can be expressed in terms of proteins, carbohydrates, fats, salts, and water; and the necessary quantities of these substances can be determined by an examination of dietaries, such as that conducted by Atwater, or by experiments upon the balance of nutrition, such as those made by Atwater, Benedict, and Rubner. The former is the more certain guide, for it represents the results of numerous experiments carried out by many individuals under the most diverse conditions.

The values of the different dietaries are expressed in terms of proteins, carbohydrates, and fats, and in calories to represent their latent energy. This method is convenient, and is, in fact, the only comparative method possible at the present time. Evidence, however, accumulates every day to show that there are some obscure substances which are essential for nutrition: pure protein, carbohydrate, fat, salts, and water, are not sufficient. The healthy man, guided by his likes and dislikes, obtains these unknown substances when they are needed, and unconsciously adjusts them by his distaste for a monotonous and limited diet.

The following table gives the results of some of the examinations

* See p. 612.

of different dietaries* in terms of protein, and the total energy of the mixed diet of protein, carbohydrate, and fat. Other tables including the quantities of the separate classes of foodstuffs are given in a former article.†

| | | Total Protein Eaten: Dry Weight. | Energy of Total Diet of Protein, Carbohydrate, and Fat. | Digested Proteins. | Energy Utilised. |
|---|---|---|---|---|---|
| | | Grammes.‡ | Calories.§ | Grammes. | Calories. |
| United States | Labourers at hard muscular work | 177 | 6,485 | 162 | 6,000 |
| | Athletes | 198 | 4,980 | 182 | 4,510 |
| | Farmers, moderate muscular work | 100 | 3,685 | 92 | 3,425 |
| | Men, little or no muscular work | 86 | 2,820 | 80 | 2,600 |
| | Very poor working people | 69 | 2,275 | 64 | 2,100 |
| Scotland | Workmen | 108 | — | 99 | 3,228 |
| | Students | 143 | — | 132 | 3,979 |
| Germany | Farmers | 137 | — | 126 | 4,530 |
| | Professional men | 111 | — | 102 | 2,511 |
| Japan | Labourers | 118 | — | 103 | 4,415 |
| China | Labourers | 91 | — | 83 | 3,400 |
| Egypt | Labourers | 112 | — | 103 | 2,825 |

It is interesting to note that these data give no support to the widely prevalent view that the natives of China and Japan need only a little rice as food, even when they are doing hard work. It is contrary to the law of the conservation of energy to expect a good output of work unless there is a good intake of food.

In the above table the weights of the different foods represent dry weights, and the physiological heat-values are for 1 gramme of dry protein, 4·1 calories; carbohydrate, 4·1 calories; and fat, 9·3 calories. With the aid of tables showing the composition of different articles of food, the energy value of any diet in terms of calories can be calculated.

The chief conditions which necessitate changes in diet are age, muscular work, and climate. Young children, in relation to their weight, require a far greater quantity of food than the adult. A boy ten years of age will eat almost as much food as his father. Children grow rapidly, and require food for the building up of new tissues. They are very active, if they are healthy, and need extra food for the supply of energy; they lose more heat from their bodies, owing to the large surface of their skins in relation to their

* Langworthy, *Food Customs and Diet in American Homes*, United States Department of Agriculture, 1911, Circular 110, p. 16.

† See p. 523. ‡ 100 grammes = 0·22 pound.

§ 1 calorie = 1·54 foot-tons (approximately).

weights, and to maintain their temperature must eat more food. The needs of infants can be properly supplied only by their mother's milk. The composition of milk varies in different animals, and bears a relationship to the varying needs and bodily compositions of the respective offspring. The following table of some of Bunge's analyses shows the close resemblance between the composition of the ash of the mother's milk and that of the suckling. At the same time it is to be noted that there is no such resemblance between the ash of the milk and that of the mother's blood or serum.

| In 100 Parts of Ash are found— | Rabbit, Fourteen Days Old. | Rabbit's Milk. | Rabbit's Blood. | Rabbit's Serum. |
|---|---|---|---|---|
| Potassium .. | 10·8 | 10·1 | 23·8 | 3·2 |
| Sodium .. .. | 6·0 | 7·9 | 31·4 | 54·7 |
| Calcium .. .. | 35·0 | 35·7 | 0·8 | 1·4 |
| Magnesium .. | 2·2 | 2·2 | 0·6 | 0·6 |
| Iron (oxide) .. | 0·23 | 0·08 | 6·9 | 0 |
| Phosphorus (acid) | 41·9 | 39·9 | 11·1 | 3·0 |
| Chlorine .. .. | 4·9 | 5·4 | 32·7 | 47·8 |

The rate of growth of sucklings of different species varies, and, as the next table shows, bears a relationship to the composition of the mother's milk (Pfoscher).

| | Time Taken by New-born Animal to Double its Weight. | 100 Parts of Mother's Milk contain— | | | |
|---|---|---|---|---|---|
| | | Protein. | Ash. | Lime. | Phosphoric Acid. |
| | Days. | | | | |
| Man .. | 180 | 1·6 | 0·2 | 0·328 | 0·473 |
| Horse .. | 60 | 2·0 | 0·4 | 1·240 | 1·310 |
| Cow .. | 47 | 3·5 | 0·7 | 1·600 | 1·970 |
| Goat .. | 19 | 4·3 | 0·8 | 2·100 | 3·220 |
| Pig .. | 18 | 5·9 | — | — | — |
| Sheep .. | 10 | 6·5 | 0·9 | 2·720 | 4·120 |
| Dog .. | 8 | 7·1 | 1·3 | 4·530 | 4·930 |
| Cat .. | 7 | 9·5 | — | — | — |

The milk of the mother supplies a natural transition from the food obtained from the mother during fœtal life to the animal or vegetable food which will be supplied later on from other sources. The milk of another animal, whether it be unaltered or modified artificially, will not be an effective substitute. The mother supplies in her milk a food which is adjusted to the needs of the infant at different ages. The milk has not the same composition during the different periods of lactation. Apart from actual food substances, the mother's milk appears to contain antibodies, enzymes, and, it

may be, bacteria, which are specific and necessary for the nutrition of the offspring. Under natural conditions an infant never obtains sterile milk, and even if it be given sterile milk, it will obtain bacteria by sucking its fists and clothes. The proper substitute for the mother's milk is not the pure or sterilized milk of a cow, but the milk of a healthy wet-nurse. The high death-rate of infants in the most civilized countries is due chiefly to the neglect of natural feeding.

The next condition which influences the need of food is muscular work. All experience and all experiments show that the quantity of food must be adjusted to the amount of work performed. A healthy man or animal living an active life does not eat too much, even if the supply of food is unlimited. A patient at rest in bed does not want much food, for his need of sources of energy for work and the production of heat is reduced. This is reflected in his small and fastidious appetite. On the other hand, a convalescent, after an acute disease, needs an extra quantity of food to replenish his reserves, which were exhausted during the inanition of fever.

Lastly, there is the important influence of climate. Cold increases the activity, the production of heat, and the appetite. Heat has an opposite effect. Nutrition, therefore, is favoured by a reasonable exposure to cold, and there is little doubt that the success of the open-air treatment of consumption depends upon this factor, and not upon the purity of the atmosphere in which the patient lives. By proper attention to the influence of climate and muscular activity, the physician is able to alter the nutrition of a patient more powerfully than by any drug or system of dietetics.

The influence of these factors has been considered chiefly in relation to the quantity of food. The quality also is important, and has been much discussed recently by Chittenden,* who maintains that most of the white races eat too much protein. He pleads for nitrogenous economy in nutrition on the ground that the kidneys and other parts of the body may be injured by the products of protein metabolism. It may be granted that a man can live upon a quantity of protein less than most men eat, but it does not follow that a minimum is the ideal. There is no evidence that the kidneys cannot respond to the demands made upon them under ordinary conditions of diet, and it might be argued that they would atrophy from disuse if they were given always the minimum amount of work to do. No organ in the body is strengthened by always shielding it from work. The exact opposite is true; it is developed by work. Constant overwork is a different condition. The strongest evidence against a minimum of nitrogen is obtained from a comparison of the dietaries of men, especially of those who have much

* *Physiological Economy in Nutrition* (London), 1905; *The Nutrition of Man* (London), 1907.

muscular work to perform. The dietaries already given* show a daily average of about 120 grains of dry protein, a far larger quantity than the amount suggested by Chittenden. Nitrogenous equilibrium can be maintained on very different amounts of protein in the food, and is not a test of the efficiency of a diet.

Fats and carbohydrates have a different position in a dietary. They contain no nitrogen, and cannot be used directly for the formation of tissue. They serve as immediate sources of energy, or are stored in the body as deposits of fat and glycogen. Carbohydrates can be converted into fats in the body, and there is evidence that carbohydrates may be formed from fat. In some measure, therefore, carbohydrates and fats are interchangeable. A decrease of the one in a dietary may be compensated by an increase in the other. As a general rule, fat is the dearer article of food, and for this reason is not abundant in the food of the poor. There is, however, a limit to this substitution of the one foodstuff by the other. Carbohydrates act as a sparer of protein, and recently there has been brought forward evidence which suggests that they are absolutely essential for endocellular synthetic processes in connection with protein metabolism (Cathcart).†

An adult animal can be kept alive upon a diet containing only one kind of protein, provided that the protein is not deficient in individual amino-acid groupings ; but young animals do not grow if they receive such a diet. A mixture of pure proteins, fats, carbohydrates, salts, and water, is not sufficient for a young animal, but the addition of very small quantities of milk or extracts of tissues to such a diet will make it efficient. The amount of these substances is so small that the action appears to be a special one, stimulating metabolism rather than supplying material for oxidation.‡ In other directions similar evidence has been obtained. A diet of polished rice is associated with beri-beri in man and polyneuritis in birds, and it has been shown that the cortical layers of rice, which are removed in the process of polishing, contain a substance which will cure those diseases. The essential substance is only present in minute amount—probably not more than 0·1 gramme per kilogramme of rice. It is an organic base, but its exact chemical nature is unknown.§ It has been called "vitamine." Scurvy, rickets, and other forms of malnutrition, may be due to the absence of such a principle.

It may be stated, therefore, that a diet cannot be valued simply by its content of protein, carbohydrate, and fat, or by the energy-value of these in calories. The only true test is furnished by its capacity to support the life of a vigorous and actively growing

* See pp. 523 and 609.

† *Journ. of Physiol.*, 1909-10, xxxix. 311 ; 1910-11, xli. 276.

‡ Hopkins, *Journ. of Physiol.*, 1912, xliv. 425 ; Osborne and Mendel, Carnegie Institution, Publication No. 156, Parts I. and II., 1911.

§ Funk, *Journ. of Physiol.*, 1911, xliii. 395.

animal. The application of such a test requires foresight and the recognition of the influence of too sudden changes in diet. It is well known in the case of animals and man that a progressive or gradual change is often necessary if digestive disturbances or toxic effects are to be avoided. The body appears to require time to adapt itself, by the production of antibodies or otherwise, to new articles of diet. There still remain personal differences or idiosyncrasies. One man's food is another man's poison—a truth of great interest in the study of immunity.*

The ordinary process of metabolism in an adult man may be considered as an intake balancing the output, the man's weight and the composition of his body remaining, as far as can be ascertained, remarkably constant. The daily loss of degenerate and dead cells is replaced by new growth. The extreme variations from this condition are wasting and fattening, and both are of great physiological and pathological interest.

**Fasting and Starvation.**—A man can live for thirty or forty days without food, provided that he receives water. This is a much longer period than would be expected from the popular idea of the effects of fasting. Undue alarm is expressed often when a patient or prisoner takes little or no food for two or three days. The danger lies not in the lack of food, but in the disorder of which the loss of appetite or the refusal to take food is a sign. The disorder may be serious or trivial, and there is evidence that in many cases the loathing of food has a protective purpose, frees the body from digestive work, and the action of the products of digestion, and affords time for rest and recovery. The exchange of material is maintained with considerable uniformity during the early days of the fast at the expense of the reserves stored in the body. This is shown by the following results† obtained in a healthy man:

| Subject. | Day. | Calories. | Body-Weight in Kilos. | Calories per Kilo., Body-Weight. |
|---|---|---|---|---|
| Medical student twenty-six years old | Last day of taking food | 2705·3 | 67·8 | 39·9 |
| | 1st day of fast | 2220·4 | 66·99 | 33·15 |
| | 2nd ,, ,, | 2102·4 | 65·71 | 32·6 |
| | 3rd ,, ,, | 2024·1 | 64·88 | 31·2 |
| | 4th ,, ,, | 1991·3 | 63·99 | 31·13 |
| | 5th ,, ,, | 1970·8 | 63·13 | 31·23 |
| | 1st day of taking food | 2436·0 | 64·0 | 38·1 |
| | 2nd ,, ,, | 2410·0 | 65·6 | 36·0 |

* See examples of toxic effects of foods, p. 182.

† Johannson, Landergren, Sondén, and Tigerstedt, *Skand. Arch. f. Physiol.*, 1896. Bd. vii., s. 51.

The fasting man obtains the nutriment which he requires chiefly from his stores of glycogen and fat, and as these diminish he draws in greater measure upon the proteins of his tissues. The fall in the respiratory quotient, $\frac{CO_2}{O_2}$, to or below 0·7, is no proof that he is living upon fat alone, for the quotient is the resultant of quotients, some high and some low, due to different oxidations. This interpretation is supported by the fact that, even after a prolonged fast, the tissues of the body are not free from either glycogen or fat. It would appear that by means of ferment action in the tissues, proteins, fats, glycogen, and salts, are taken from the less active organs to supply the needs of those parts, such as the heart, respiratory muscles, and brain, upon the continued activity of which life depends. In this way nutriment will be supplied by the blood, and decomposition and synthesis of all classes of food material may continue. Even under adverse conditions the body remains economical, and as far as possible preserves its most vital organs. The supply of one tissue by another is not to be looked upon as a new process, but as the accentuation or unmasking of a normal one.

Lack of water causes great distress, and brings death more rapidly. The tissues of the body contain about 70 per cent. of water, and there is a daily loss by the urine, breath, fæces, and sweat. Large fluctuations in the weight of the body can be brought about by changes in the intake or output of water, but they are of a temporary nature. Sweating produced by vigorous exercise on a hot day may result in the loss of 2 litres of water in an hour or two, but the great thirst so caused leads to a speedy replenishment of the water stored in the tissues. Copious drinking, on the other hand, is followed by greater excretion of water in the urine.

Further details of the metabolic changes during fasting are given in the discussion of fever,* one of the pathological conditions in which fasting plays a great part. The retention of water is considered in connection with œdema.†

**Fattening.**—The opposite condition to fasting is the one in which the intake exceeds the output and the individual increases in weight. Over short periods this may be due to water, but when it persists for days, or even years, it is caused by growth or the deposition of fat. In the young and growing animal the progressive increase in weight is due to all the tissues, but in the adult to the deposition of fat alone. The cause of obesity is in most cases insufficient muscular work rather than excessive eating. Men and animals doing a considerable amount of regular work do not become fat, even if they eat as much as they desire. A corpulent constable in rural districts is the rare exception, whereas among policemen

* See p. 513. † See p. 326.

on "point" duty in a large city the reverse is the case. The presence of corpulent soldiers in a company is sufficient proof that the officer has not trained his men for active service in the field. Although this relationship between the deposition of fat and muscular activity is true, it must be allowed that the problem is more complex. The peculiar activities of the cells of the body are the chief factor, and attention must be drawn to the conditions which influence them.

There is no doubt that the extensive experience of farmers upon these questions is of extreme value, and is applicable to the conditions in man, notwithstanding the mistaken but popular idea that man by the progress of civilization is escaping from biological laws. The farmer recognizes the following conditions as favourable to fattening. In the first place there are individual tendencies to fattening, and the breed must be selected. Jersey cows do not fatten well, even when they have ceased to yield milk, but cows of the Shorthorn and Sussex breeds fatten readily. In the domestic animals the deposition of fat is encouraged as much by diminishing their activity as by increased or forced feeding. In addition to inactivity there must be contentment. The disturbing effect of sexual activity is removed in the males by castration, and in the females by finishing the fattening process in the early months of pregnancy. The animals do not fatten well unless they enjoy their food. Sufficient variety is needed, and if the food is not very palatable, condiments are added.

Should the farmer need to promote growth in frame and muscle as well as fat, he leaves the young animal free to give way to its natural instincts to gambol and roam in the fields. He also prolongs the active growth of the bones by castration. The ox is larger than the bull of the same breed. The season of the year is also important. Wild animals increase their deposits of fat when the breeding season is over, and their food is still plentiful. They thus store up reserves, upon which they can call during times of scarcity in a severe winter. The layer of fat also forms an extra protection from the cold, and the additional heat produced by the muscular activity necessary to support the increased weight of the body is no disadvantage in winter. The winter quarters of the year are, in the case of full-grown animals, the favourite ones for fattening for the market.

If we apply this country knowledge to the subject of obesity in man, a close agreement is found. There is beyond question an individual tendency to deposit fat. Some men never become fat, even if they eat more than they need, or do but little muscular work; others find that they must be constantly on their guard to so adjust their food or muscular exercise that fat is not deposited in excess, or discover, by a change of circumstances which forces them to do a regular amount of hard muscular work, that they

can eat as much as they desire without increasing their weight. Contentment is a factor, and by popular agreement cheerfulness is associated with fatness and anxiety with leanness. The influence of the sexual glands appears to be the same as in the domestic animals. Eunuchs are said to be large in frame and fat, and in women there is a tendency to deposit fat during pregnancy, and especially after the menopause.

The young child is a young animal, and for its proper development should be treated as such. Model dwellings, free meals, and free education, will not prevent physical degeneration in the children of the poor. Frequent opportunities for play or healthy work in the open air are as important. The activity of the living cells of the body, not the supply of food, determines growth.

Obesity entails considerable disadvantages. The fat man has to carry an increased weight, and therefore does work under uneconomical conditions. His temperature is raised readily, and sweating and fatigue make him disinclined to active work. His breathing is hampered by his corpulent abdomen, and this will in turn impair the efficiency of his heart. To avoid discomfort, he does less work. Thus a vicious circle is formed, the deposition of fat being favoured by the inactivity. A change of diet to one consisting chiefly of protein is the general treatment of such cases, and is the basis of the Banting system. Protein, as compared with carbohydrate and fat, has a stimulating effect upon the exchange of material in the body; moreover, in order to obtain the necessary energy, the man will have to draw upon his reserves of fat. Extracts of thyroid gland have been used successfully in some cases to increase the exchange of material, and it has been suggested that a slight degree of thyroid insufficiency is one of the causes of obesity.

The disease known as *adiposis dolorosa* is characterized by the presence of isolated fatty swellings in the subcutaneous tissue of various parts of the body. These swellings are very painful, especially when the patient moves. There may be, in addition, a diffuse deposit of adipose tissue, great muscular weakness, and mental apathy. Post-mortem examinations in some cases of this rare disease have shown pathological changes in the thyroid gland.

## INTERNAL EXCHANGE—THE INTERNAL SECRETIONS OF DUCTLESS AND OTHER GLANDS.

The view that glands and other organs of the body contain substances which influence the physical and mental condition is very ancient and widespread, and its practical application in modern organo-therapeutics is but the revival of a primitive method of treatment. The discovery of a glandular product which was

discharged, but not by the duct of the gland, led to the modern knowledge of "internal secretion." In 1855 Claude Bernard discovered the glycogenic function of the liver, and called it the "internal secretion" in contradistinction to the "external secretion" of the bile. The use of the term was extended by Brown-Séquard and Schiff to the formation of useful products by the ductless glands, the secretions of which reach the vascular system either directly or through the lymphatics. A further extension is taking place, for every cell of the body appears to retain in some measure the power of a primitive cell—the capacity of producing secretions or excretions which influence other cells. Thus the interaction of one part of the body upon another becomes so complex that the entire body must be considered the physiological unit. The functions of the parts can be studied rightly only in relation to the whole. The disease or removal of one part will produce effects which will indicate the function of the part, but even in this case the result cannot be considered a pure one, for the animal will attempt to compensate for its loss. This inherent defect in the method can be minimized by a study of the natural variations in the glandular activity, and the effects produced by injections of extracts of the glands.

These internal secretions can influence the development, growth, and nutrition of the body so profoundly that their action has been compared to that of potent drugs. Extracts of various organs, such as thyroid extract and adrenalin, are used extensively now with beneficial results. It is necessary, however, to remember that this modern practice is a return to an ancient method of treatment, which was still in vogue among savages in recent times, when it was ridiculed by the highest medical opinion of civilized nations.

A most important advance in the conception of "internal secretion" was effected by the discovery by Bayliss and Starling of *secretin*,* the chemical stimulus, or "hormone," which, absorbed from the duodenum by the blood, is carried to the pancreas, and evokes a secretion of pancreatic juice. At the precise moment when it is wanted, the secretion is formed from a precursor by the action of the acid food on its discharge from the stomach into the duodenum. Thus the co-ordination of the processes of the body may be effected by chemical as well as by nervous stimuli. Indeed, it has been suggested that nervous impulses may act by setting free active chemical substances.

A chemical agent may increase or diminish chemical changes in the body, and different effects may be produced by the same substance in different concentrations. Further, the absence of the given chemical substance may result in abnormal changes. From a chemical point of view, health and disease may be considered as

* See p. 597.

the resultant of various chemical changes, which are influenced by numerous factors. In some individuals there may be obvious chemical abnormalities* which persist throughout life, such as alcaptonuria and cystinuria. In others a peculiar constitution or diathesis of a recognized type may be accompanied by chemical differences as yet unrecognized. Chemical change may be altered by various physical and chemical agents. Herein lies the foundation of scientific therapeutics.

The subject of "internal secretions" has become so great that it is impossible here to give more than a mere outline of the evidence in connection with the different glands.†

**Thyroid and Parathyroid Glands.**—Most of the knowledge of these glands has arisen within the last forty years, and it is possible now to make a comparison between the experimental and clinical results. The complete removal of these glands in cats is followed within two or three days by twitching of the muscles, spasms, and epileptiform convulsions. There is depression, loss of appetite, and wasting. Within a week the animal dies. In exceptional cases, which may be due to small accessory glands, there is no acute disturbance, and the animal passes into a chronic condition of malnutrition or cachexia.

On the clinical side there is a close agreement with the experimental results. The early operations for the relief of goitre in man showed that complete excision of the enlarged gland produced in some patients an acute condition of *tetany*, in others a disorder of nutrition, now known as operative *myxœdema* or *cachexia strumipriva*. The latter disease in some respects resembled *cretinism*, although, owing to the fact that growth had ceased, there was no great deformity. In the congenital cretin there are characteristic abnormalities. His stature is stunted; a patient of thirty years of age may be less than three feet high. The body is deformed, the limbs are short and misshapen, the chest is narrow, the abdomen large and pendulous, and the neck and shoulders are swollen by large pads of fatty tissue. The head is broad, the nose is flattened, and from the large mouth the tongue often protrudes. The skin is dry, wrinkled, and of an earthy colour, and the hair is coarse, sparse, and dry. The mental condition is equally defective. The cretin is generally an idiot.

In adults a cretinoid condition was discovered by Gull in 1873. The patient shows a great loss of bodily and mental energy; the features and hands become disfigured and apparently œdematous. There is, however, no true œdema, but a collection of newly-formed connective tissue under the skin. For this reason the disease is called "*myxœdema*."

* See Chapter XVI., p. 654.

† See Swale Vincent, *Internal Secretions*, 1912; and Biedl, *Innere Sekretion*, 1910, in which full references are given.

All of these conditions are associated with disease or absence of the thyroid gland, and are improved greatly, or even cured, by treatment with thyroid extracts. The administration of the active constituent of the gland must be continued throughout life—a fact which indicates that the body requires a constant supply of some substance present in the healthy gland. The results of removal or disease of the gland in man and animals are complicated by the fact that in many cases the parathyroid glands are bound up closely with the thyroid, and in others accessory thyroids or parathyroids may escape removal. The parathyroid glands are small masses of cells, some of which contain colloid, but not in any alveolar system. According to some observers, they can develop into thyroid tissue; others, on the contrary, maintain that they are glands of a distinct and separate order. There is a conflict of opinion also upon the effects of removal of the glands, for it is clear that the results of earlier observers may have been mixed ones, owing to the fact that parathyroid and thyroid were removed at the same time. The balance of evidence inclines to the view that the parathyroid produces a secretion which influences the nervous system, *tetany* being produced by removal of the gland, and *paralysis agitans* by a chronic deficiency of the secretion. An increased secretion of the parathyroid is considered to be the cause of the symptoms in *exophthalmic goitre* (Graves's or Basedow's disease). In a similar way the absence or inefficiency of the secretion of the thyroid gland is held to be the cause of *cretinism* and *myxœdema*, and an excess of secretion as the disturbing factor in goitre. Adiposis dolorosa* and other conditions of disordered nutrition may be due to defective secretion of the thyroid glands.

There are two chief theories of the action of these glands. According to one, the glands neutralize poisonous metabolites produced in the body; whereas the rival theory maintains that the glands are true secreting organs, supplying in the colloid a peculiar combination of iodine and protein—*iodothyrin*. The evidence increases in favour of the latter theory. Apart from clinical evidence of the benefit produced by thyroid extract in cretinism and myxœdema, experiments have shown that the extracts increase the metabolism of the body, whereas disease or removal of the gland diminishes it. How the active principle acts, whether directly on the tissues or indirectly through the nervous system, it is impossible at present to say. In large doses the thyroid extract produces, both in men and animals, toxic effects, such as tachycardia and glycosuria, and, if continued, a condition resembling exophthalmic goitre may result.

**Suprarenal Glands.**—The function of these glands was unknown until Addison, in 1855, showed that a definite disease—now known by his name—was associated with pathological changes in the glands. The characteristics of this disease are loss of muscular

* See p. 616.

strength, apathy, digestive and nervous disturbances, such as vomiting, diarrhœa, convulsions, and coma; at the same time there is a pigmentation or bronzing of the skin and parts of the mucous membranes. Addison's discovery has been, and is frequently, confirmed, and it is now known that the disease is generally tubercular in origin.

The next great advance in the knowledge of these glands did not occur until fifty years had passed. Oliver and Schäfer discovered that the medulla of the gland, but not the cortex, contained an active principle, which, in very small doses, produced a great rise of blood-pressure. Previous investigations of the development, comparative anatomy, and minute structure of the suprarenal gland, had proved that it consisted of two distinct parts—cortex and medulla. The cortex is derived from the mesoblast, is separate, in some fishes, from the medulla, and is characterized by the presence in its cells of lipoid granules; the medulla of the gland is an outgrowth or development of the sympathetic system, its cells stain deeply with chromates, and give a green colour with iron salts. This chromophile or chromaffine substance is characteristic of the medulla in all vertebrates. In this and other respects the medulla resembles the *paraganglia*, or chromophile bodies, such as the carotid and coccygeal glands, which are found in close association with the sympathetic system in different parts of the body. This relationship is significant, for the effects of extracts of the medulla of the suprarenal gland are precisely those of stimulation of the sympathetic.

The functions of the two parts must be considered in detail, and in the first place those of the medulla, for much less is known about the cortex. Removal of the whole gland, owing to its double structure and function, does not give an adequate analysis, but shows, nevertheless, how essential the gland is to the organism. The duration of life in dogs after this operation is from two hours to two days; there is muscular weakness, apathy, and paralysis, but no pigmentary change has been observed. If only one gland be removed in a young animal, compensatory hypertrophy occurs in the other, indicating that the gland is constantly at work. Attempts have been made to counteract the effects of loss of the glands by extracts or transplantation of the glands, but the results both in men and animals have been discordant. Much more light has been thrown upon the function of the gland by a study of the effects produced by extracts of its substance.

Extracts of the medulla contain an active principle—adrenalin—which, even in such small doses as 0·001 milligramme per kilo. of body-weight, will produce a characteristic rise of blood-pressure. This is only one of the effects, for the researches of Langley, Elliott, Dale, and others have shown that the effects are those of stimulation of the sympathetic, whatever they may be upon the different parts of the body; thus there may be either constriction or relaxa-

tion of involuntary muscle fibre. The adrenalin acts upon the myoneural junction, upon a reactive material, or receptive substance.

In large doses adrenalin has a toxic effect, producing in man palpitation and headache; in dogs, rabbits, and guinea-pigs a dose of 0·1 to 0·2 milligramme per kilo. of body-weight is fatal. Long-continued administration of non-lethal doses produces a condition of arterio-sclerosis.* Other effects of the administration of adrenalin are hyperglycæmia and glycosuria,† and a rise of temperature. The drug appears to act upon the pancreas, diminishing its activity as a gland producing an internal secretion. These conditions have been compared with the diabetes and hyperthermia produced by puncture of the so-called "diabetic" and "heat" centres.

Adrenalin has not only been prepared in the pure condition and shown to have the formula given below,‡ but it has also been synthesized in two forms—one active, the other inactive. Tyrosin is considered to be a mother substance of adrenalin, and it has been suggested that the pigmentation seen in Addison's disease is due to the conversion of tyrosin into a pigment by the action of oxidases in the skin and mucous membranes.

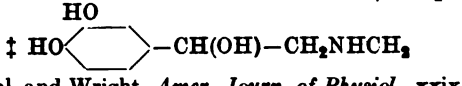
The body is constantly receiving small doses of adrenalin, for its presence can be shown in the venous blood leaving the gland. The tone of the whole sympathetic system is maintained by the action of these repeated doses, and since the secretion is under the control of the sympathetic system, a more abundant discharge may be effected by nervous impulses passing to the gland. In this way emotional disturbances, such as rage or fright, may lead to an excessive discharge of adrenalin, and glycosuria§ may be produced. Such experimental results will probably have a great significance in the future, for therein would appear to be the scientific explanation of the disorders which are said to start from fright or other emotional disturbance. On the other hand, the good effects of contentment, amusement, sport, and games may in part be due to the influence exerted by the internal secretions liberated by nervous impulses.

Adrenalin has all the characteristics of the hormones described by Starling; it does not cause the production of antibodies, which would neutralize its influence; it is susceptible of easy passage through the walls of the bloodvessels; and its effect upon the body is transient, owing to the ease with which it is destroyed by oxidation, or in some cases removed by excretion in the urine.

*The Cortex of the Suprarenal Gland.*—The function of this portion of the gland is obscure, but there is evidence pointing to the formation of an internal secretion, which influences the sexual glands.

* See p. 301.

† See p. 673.

‡ 

§ Cannon, Shohl, and Wright, *Amer. Journ. of Physiol.*, xxix. 280, 1911.

Observations* upon the comparative anatomy of the gland have shown that in some species the cortex is more developed than the medulla; in others the reverse is found. The relatively great size of the cortex is characteristic of the gland in mammals. The medulla grows until puberty, and then remains stationary throughout the remaining years of life, unless gestation occurs; the cortex, on the other hand, continues to increase. Both portions of the gland undergo an acceleration of growth if the animal becomes pregnant. The microscopical structure of the cortex shows the presence of lipoid granules in the cells, and it has been suggested that these exert an antitoxic action by combining with poisonous substances formed in the body or introduced from outside.

Hyperplasia or tumours† of the cortex in females are usually associated with a diminution of certain female characteristics and the development of some of those of the opposite sex. The converse rarely occurs. In some patients with retarded sexual development or rapid loss of function, the suprarenals have been found atrophied; on the other hand, in Addison's disease changes have been described in the generative and interstitial cells of the testes.

**Pituitary Gland.**—This gland‡ consists of two lobes, an anterior and a posterior; the former is derived from the epithelium of an upgrowth of the buccal ectoderm, and the latter from a downgrowth of the floor of the third ventricle of the brain. The anterior lobe is composed of glandular cells, but the posterior lobe is formed almost entirely of neuroglia. A further distinction must be made between two parts of the anterior lobe, the pars anterior and the pars intermedia, which are separated in some animals by the intraglandular cleft. The characteristic feature of the cells of the intermediate part is the hyaline or colloid material which is present in the form of globules. This substance appears to be formed by a transformation of some of the protoplasm of the cells and to find its way into the third ventricle and also into the other portions of the gland. After thyroidectomy the colloid material is increased, but it has a different physiological action to that of iodothyrin, and contains no iodine.

The function of the gland has been investigated by excision and by the administration of extracts of the different lobes. According to most observers, total removal of the gland is usually followed by death within a day or two. The operation is a difficult one, but control experiments, in which the same procedure, with the exception of removal of the gland, was performed, gave negative results. Other observers§ maintain that no bad effects follow excision.

* Elliott and Tuckett, *Journ of Physiol.*, xxxiv. 332, 1906.

† Glynn, *Quart. Journ. Med.*, v. 157, 1911-12. Here numerous references are given.

‡ Schäfer, *Textbook of Microscopic Anatomy*, p. 689, 1912.

§ Horsley and Handelsmann, *Brit. Med. Journ.*, vol. ii., November 4, 1911.

In man Marie showed a relationship between hypertrophy, or tumours of the gland, and an abnormal growth of the body. The lower jaw, hands, feet, ears, and nose grow to a great size, and in young subjects the stature and build of the body are those of a giant. The condition is known as *Acromegaly*, and is accompanied by headache, impairment of sight, and polyuria. It appears that the overgrowth is due to an excessive secretion of a hormone in the hypertrophied anterior lobe, the polyuria to an excess of the secretions of the pars intermedia and the posterior lobe, and the defective sight to the pressure exerted by the growth upon the optic chiasma.

These views are based upon the results* which have followed the injection or administration of extracts of the different lobes. With extracts of the posterior lobe and pars intermedia, a rise of blood-pressure is produced and an increased flow of urine. The bloodvessels of the kidney are dilated, but the diuresis is not due entirely to these vascular changes, for they may be absent in special cases. A second or third dose of the extract will produce a fall of blood-pressure, but still the diuretic effect is seen. In man it has been proved that this diuresis follows the administration of the gland, and it has been suggested that the polyuria and glycosuria which occur in some cases of injury to the skull are due to an excessive secretion from the posterior lobe of the gland.

A substance resembling in action the extract of the posterior lobe has been discovered in the cerebrospinal fluid,† and this supports the view of Herring that the colloid material of the pars intermedia is secreted into the cavity of the third ventricle of the brain.

Feeding experiments with the anterior lobe have given no definite evidence of abnormal growth in young animals, and the same is true for grafts. If, however, the posterior lobe with the pars intermedia is used in such experiments, polyuria is produced.

Further evidence of the complex function of the pituitary gland is afforded by the experiments of Schäfer‡ and Mackenzie.§ Extracts of the posterior lobe produce a very distinct galactogogic effect. The active substance is not destroyed by boiling, is soluble in water, but insoluble in alcohol; its chemical nature is unknown. It is present in the pituitary not only of lactating and non-lactating females, but also of males; it is not specific to the mammalian gland, for it is present in the pituitary gland of birds. Hypertrophy of the gland is said to occur during pregnancy; in cats the increase in size may be more than 15 per cent.

The active principles of the pituitary gland appear to act directly

* Oliver and Schäfer, *Journ. of Physiol.*, xviii. 277, 1895; Schäfer and Swale Vincent, *Ibid.*, xxv. 87, 1899-1900; Schäfer, *Die Funktionen des Gehirnanhanges, Berner Universitätsschriften*, Heft 3, 1911.

† Cushing and Goetsch, *Amer. Journ. of Physiol.*, xxvii. 60, 1910-11.

‡ Proc. Roy. Soc., B. 84, 16, 1911.

§ *Quart. Journ. Expt. Physiol.*, iv. 305, 1911.

upon the gland cells, for it is noteworthy that in the kidney and the mammary gland there is no satisfactory evidence of secretory nerves.

**Generative Glands.***—The best examples of internal secretion are found in the generative glands of the two sexes. The effects of removal of the testes have been known for centuries, for the operation has been practised on man and animals by civilized and uncivilized races from the earliest times. For many years also naturalists have accumulated observations upon the relation of secondary sexual characteristics to the activity of the generative glands. The fundamental importance of this knowledge is often ignored, and attempts to apply it in relation to certain aspects of modern civilization are resisted with contempt. The evidence, nevertheless, is clear. The welfare of the individual as much as the welfare of the race is bound up with the normal activity of all parts of the body.

*Male Generative Glands—Testis.*—Two kinds of cells can be recognized in the testis, the mother-cells of the spermatozoa and the interstitial cells. The former degenerate after ligature of the vas deferens or exposure to the Röntgen rays; the latter remain intact and produce, it has been suggested, the internal secretion peculiar to the testis.

The development of the testis at puberty is associated with the appearance of the male secondary sexual characteristics, such as the growth of hair on the face and the "breaking of the voice," due to the increased growth of the larynx. The removal of the testes in early life prevents the development of these characteristics, and the individual approximates to a type intermediate between the male and female. The epiphysial cartilage does not ossify so early, and a greater growth of the bones occurs. The accessory male glands, the prostate, and the vesiculæ seminales, fail to grow. The temperament is more placid and there is an unusual deposition of fat. Hair on the face is scanty or absent, and the voice remains that of a boy; indeed, castration was employed in times past to preserve the voices of choristers.

In animals the results of castration are well known. There is a greater growth of bone and a greater tendency to fatten. The ox is bigger than the bull of the same breed, and its horns are much longer but not so strong; it is far more docile. In deer there is, as John Hunter showed, an interesting relationship between the testes and the horns, for if the animal is castrated after the horns have been shed they will not be renewed; on the other hand, if the operation is performed while the horns are intact they remain permanently, and are not shed as they would be in the natural condition.

* Marshall, *Physiology of Reproduction*, 1910; and Loewy, *Ergebnisse der Physiologie*, 1 Abt., S. 130, 1903. Here numerous references are given.

The marriage plumage of birds is connected with a seasonal growth of the testis, and in capons the male type of plumage, spurs, and gills is absent. In many birds the young males and females are not distinguished by different plumage until the sexual glands are fully developed.

The respiratory exchange is diminished in castrated animals; this is to be associated with the increased tendency to deposit fat. The changes of temperament which coincide with the maturity, periodical activity, and atrophy of the sexual glands, are well known.

These various effects of the internal secretion of the testis are confirmed by the results which have been obtained with testicular extracts. Stated briefly, the extracts prevent or remove the effects which otherwise follow castration. Poehl maintains that spermin, $C_6H_{14}N_2$, is the active principle.

*Prostate and Vesiculæ Seminales.*—The function of these organs is obscure, but there is some evidence to show that the secretions have a direct effect upon the spermatozoa, and act also as an internal secretion upon the female. The removal of the seminal vesicles of mature rats does not lessen their virile power, but diminishes to a great extent their fertility; if the prostate is removed also, intercourse is quite unfruitful. It is maintained that extracts of prostate exert a beneficial effect in some of the disturbances of nutrition seen in hysterical women.

The development of the prostate depends upon the testis, and atrophy follows castration. This operation has been done in man as a means of relief of hypertrophy of the prostate. Section or ligature of the vas deferens has been performed for a similar purpose, but the results are less satisfactory. The explanation appears to be found in the survival of the interstitial cells of the testis.

*Female Generative Glands—Ovary.*—The influence of the internal secretions of the ovary upon the female is even more pronounced and complex than that of the testis upon the male. The ovary passes through three phases—the early inactive stage before puberty, the active stage lasting from puberty until the menopause, and the stage of senile atrophy. The second or active stage shows periodical changes in the non-pregnant female, and a special growth of the corpus luteum when pregnancy occurs. The relationship of ovarian activity to the production of an internal secretion is shown in the development of the secondary sexual characteristics at puberty and the onset of menstruation and fertility. The progressive atrophy after the menopause is associated with the final cessation of menstruation, psychical disturbances, sterility, an increased tendency to deposit fat, and in some cases a sparse growth of hair upon the face.

The complete removal of the ovaries has such far-reaching effects that it is justified only in rare cases. The effect varies according

to the age of the patient. Performed early in life, spaying prevents the development of the secondary sexual characteristics, and the individual approximates to a type intermediate between the female and male. The uterus and the mammary gland do not develop, menstruation never appears, and the ossification of the epiphysial cartilages is retarded. The build of the body may be big and strong, but it is masculine in type. If the operation is performed after puberty, the uterus atrophies and menstruation is abolished. An artificial and premature menopause is the result.

The influence of the ovaries upon the body generally, and especially upon the uterus and the mammary glands, can be explained only as the result of an internal secretion, and since these changes have such a definite periodicity and relation to the discharge of ova, it is necessary to consider what element of the gland may supply the secretion. The ovary, in addition to its follicles, contains in its stroma epithelioid interstitial cells, connective tissue, and plain muscle fibres. The interstitial cells probably arise from the original germinal epithelium. The most important structure in relation to the question of the internal secretion is the *corpus luteum*. After the discharge of an ovum the cells of the follicle hypertrophy and give rise to the luteal cells, which undergo mitotic division; other luteal cells appear to take their origin from the interstitial cells, and with those arising from the follicle form the corpus luteum. If conception does not occur, this "false" corpus luteum atrophies, but if pregnancy follows, the luteal cells grow very rapidly during the early months and form the "true" corpus luteum.

The function of the luteal cells appears to be the production of an internal secretion which influences the uterus and the mammary gland. If the ovaries are removed in the early stages of pregnancy abortion follows, but not if the operation is performed at a later stage. The mammary gland shows some signs of activity at the menstrual periods, and during pregnancy it undergoes a progressive development which becomes more rapid a week or two before parturition. The stimulus is in the first place to be found in the corpus luteum of the ovary, and later in the withdrawal of milk by suckling or milking. The evidence for this is partly direct and partly indirect by the exclusion of other possible causes. The destruction of the corpora lutea or the removal of the ovaries is followed by a cessation and regression of growth of the mammary gland. If the formation of a corpus luteum be experimentally induced in an ovary, growth of the mammary gland follows, and extracts of the luteal cells act as a galactagogue. The first growth of the mammary gland at puberty or œstrus occurs after the formation of a corpus luteum even apart from pregnancy. Milk is produced by the lowest mammals, the monotremes, in which there is ovulation but no pregnancy, and in the marsupials the young fœtus is

born at an early stage, and is transferred to the mother's pouch. In the marsupial *Dasyurus* practically the whole of the formative growth in the mammary gland occurs before the formation of the placenta.* The view that the hormone to the mammary gland is supplied by the fœtus will not explain, moreover, the numerous cases of lactation in virgins and males, both among men and animals. In the first of these cases the stimulus appears to be the "false" corpus luteum and suction, and in the second suction alone. In male infants for a few days after birth a small secretion of milk is not uncommon, and is well known as "witches' milk"; it may be due to the absorption of some of the luteal extract of the mother during fœtal life.

The theory that the activity of the mammary gland is produced reflexly by nervous impulses from the ovary or uterus is disproved by the experiments of Goltz and Ewald, who showed that after section or removal of the lumbar spinal cord, bitches conceived, gave birth to healthy pups at full term, and suckled them. In women paraplegic from fracture of the spinal cord in the dorsal region similar evidence has been obtained. Section of the nerves supplying the mammary glands does not prevent its secretory activity, and stimulation of the cut nerves has given no definite results. Transplanted ovaries will exert a trophic influence upon the uterus, and in this way menstruation has been produced in women and apes. Moreover, mammary glands transplanted in animals secrete milk if pregnancy and parturition occur. In both of these cases of grafting the nerves would be destroyed, but the stimulus could be conveyed from the ovary by the blood.

The view that the placenta supplies the essential hormone to the mammary gland is disproved by the absence of a placenta in monotremes and by the cases of secretion of milk in virgins and males.

Further evidence of the close association between the activity of the ovary and the mammary gland is afforded by the transient disturbance produced in the secretion of milk by menstruation in nursing mothers and by œstrus in cows. In many, but by no means the majority of, women menstruation is absent during the first eight months of suckling, and there is a widely spread belief that suckling in this way acts as a natural protection against too rapid conceptions. In cases of malignant disease of the breast in young women, removal of the ovaries has been performed with some success to retard the progress of an inoperable growth.

The nature of the active substances in the ovary is unknown, but extracts exert a trophic effect upon the uterus and increase the respiratory exchange not only in spayed females, but also in castrated males. Osteomalacia has been treated by removal of

* O'Donoghue, Proc. Physiol. Soc., *Journ. of Physiol.*, xliii., p. xvi, 1911-12; *Quart. Journ. Micro. Scien.*, 1911.

the ovaries, and, according to some observers, the ovarian extracts increase the discharge of calcium and phosphorus in the urine.

A candid examination of the evidence leads to the conclusion that the effects of the generative organs upon the body and mind of the female are so far-reaching that on physiological grounds alone the artificial prevention of pregnancy is as much a crime against the women as against the race.

**Thymus.**—The functions of this ductless gland are obscure. In structure* it resembles in many respects a lymphatic gland; its leucocytes show signs of mitotic division, but are not collected together in germ-centres. The characteristic concentric corpuscles, or Hassall's corpuscles, appear to be degenerate cells derived from the original epithelial tube from which the thymus is developed. The gland generally undergoes atrophy about the time of puberty, but great variations in its size have been observed in different individuals of the same age.

Excision of the thymus† has yielded no conclusive results. Some observers have found no influence upon the growth or general condition of the animals; others conclude that the gland produces an internal secretion which affects the growth of the bones and the sexual organs. There is some relationship‡ between the thymus and the generative glands, for castration in cattle causes a persistent growth or a retarded atrophy of the thymus, and a similar effect has been observed in guinea-pigs and rabbits. In bulls and unspayed heifers the normal atrophy of the thymus gland, which begins after puberty, is greatly accelerated if the animals have been used for breeding. There appears, therefore, to be a reciprocal action between the thymus and the testis or ovary, each checking the growth of the other.

Injections of extracts of thymus will produce a fall of blood-pressure and a toxic effect, but these effects do not appear to be specific, for they are produced by extracts of many other tissues. The toxic effect is due to intravascular clotting, and is not produced if the coagulability of the blood is removed by leech extract before the injection.

In man a condition known as *status lymphaticus*§ has been frequently described as the cause of sudden deaths which could not otherwise be explained. Infants and young children have died suddenly, and no abnormality could be found except a great development of the thymus and lymphatic glands. In other cases older patients have died during slight anæsthesia for minor operations, and a hyperplasia of the thymus and lymphatic glands has

* Schäfer, *Textbook of Microscopic Anatomy*, p. 676, 1912.

† Noël Paton and A. Goodall, *Journ of Physiol.*, xxxi. 49, 1904.

‡ Henderson, *Ibid.*, 222; Noël Paton, *Ibid.*, xxxii. 28, 1905.

§ See Discussion *Proc. Roy. Soc. Med.*, iii., Part I., 1910 (Section of Anæsthetics, p. 19). Here references to the subject are given.

been given as a contributory cause of death. The debility and low power of resistance shown by such patients have been attributed to an intoxication produced by the abnormal growth of the thymus and other lymphoid tissues in the body. Further evidence, however, is necessary upon these points, for healthy infants and young children have a large thymus; but if they die of wasting diseases, the gland may have atrophied. Apart, therefore, from the examinations of healthy infants and young children after sudden death from accidents, there are no opportunities for the collection of data upon which to base standards for the size of the gland at different ages.

**Pineal Gland.**—This gland represents in mammals the rudimentary median eye which is better developed in some reptiles. It is composed of tubes and saccules lined by epithelium and containing earthy salts, the so-called "brain sand." There are numerous nerve fibres, but no nerve cells.

Removal of the gland has given no definite results in adult animals, and extracts have no effect upon the heart, blood-pressure, respiration, intestines, or kidney. Tumours of the gland have been found to be associated with precocious puberty, a rapid growth of the body, the sexual organs, and hair upon the face.

## CHAPTER XV

# THE METABOLIC DISTURBANCES WHICH RESULT FROM HEPATIC DISEASE

By ARCHIBALD E. GARROD

The liver plays so conspicuous a part as the greatest laboratory gland of the body, and is the seat of so many important chemical changes, that one would naturally expect profound metabolic disturbances to be brought about when this organ becomes the seat of disease. That such disturbances, important though they be, are less striking than might be anticipated is in part due to the fact that as long as a portion of a gland retains its functional activity its functions are to a great extent carried on, whereas disease which very gravely impairs the activities of the liver is not compatible with prolongation of life.

It will be well to consider the chemical pathology of hepatic diseases under two main headings, and to discuss first the effects of biliary obstruction, and in the second place those of morbid conditions of the parenchyma, upon the chemical processes of which the liver is the seat.

1. **Effects of Biliary Obstruction — Jaundice.** — Jaundice is a symptom which owns a great variety of causes. In many cases it has its origin in an obstruction of the common bile-duct. Such obstruction may be brought about by catarrh of the duct, by impaction of a gall-stone, by pressure upon the duct from without by a tumour in the hilum of the liver, or by carcinoma of the head of the pancreas.

Diseases of the liver itself may also give rise to jaundice, as, for example, acute yellow atrophy, cirrhosis, and malignant growths. Again, jaundice may result from circulatory disturbances in the liver, as in the familiar variety which is associated with chronic congestion in cases of grave cardiac disease.

In another large group of cases the origin of the jaundice is not to be traced to any gross lesion of the liver or bile-ducts, but to the action of toxic substances. These toxins are for the most part hæmolytic poisons. To this class may be referred the jaundice which occasionally follows paroxysms of hæmoglobinuria, that met with in the course of acute febrile diseases, and that due to

administration of such poisons as arseniuretted hydrogen and toluene diamine.

Although the conversion of blood-pigment into bile-pigment has not yet been effected outside the body, there can be no doubt that hæmoglobin is the parent substance of the colouring matters of the bile. The evidence in support of this proposition is in part clinical and in part experimental. Thus, Minkowski and Naunyn[1] showed that the removal of the liver of a goose, or its exclusion from the circulation, was followed by a suspension of the excretion of bile-pigment. When to a normal goose arseniuretted hydrogen, a powerful hæmolytic poison, was administered, there followed an increased excretion of biliverdin. When, on the other hand, a goose deprived of its liver was so poisoned, hæmoglobin appeared in the excreta. This is in accord with the well-known observation that any hæmolytic poison administered as such to animals, or produced in the body in disease, causes an increased formation of bile-pigment, a biliary pleiochromia. When, however, the dose is excessive, and the power of the liver to effect this conversion is overtaxed, hæmoglobinuria results. Even when the dose does not suffice to induce hæmoglobinuria, hæmoglobin may be present as such in the bile.[2] Such pleiochromia explains the slight degree of jaundice which is sometimes observed after the paroxysm in cases of paroxysmal hæmoglobinuria.

Evidence of another kind is supplied by the identity or very close similarity of hæmatoidin and bilirubin.[3] Hæmatoidin is undoubtedly a derivative of hæmoglobin, and the play of colours displayed in a contused area bears further testimony to the origin of bile-pigments from hæmoglobin, and also shows that this conversion may take place elsewhere than in the liver. Moreover, from hæmoglobin and from bilirubin alike there may readily be obtained, by the action of reducing agents, pigments which are members of the urobilin group. This designation is deliberately applied to these products, because, although they share the main properties of urobilin, they differ among themselves in minor respects, and of them the reduction product of bilirubin alone has been shown to be identical with the natural urobilin of urine.[4] Although, for reasons stated above, it must be conceded that bile-pigment can be formed from blood-pigment without the intervention of the liver, all the evidence which has accumulated of recent years tends to show that such extra-hepatic conversion never takes place on any large scale, and that no clinical variety of jaundice is in a strict sense hæmatogenous, as distinguished from hepatogenous.

Even those varieties of jaundice in which the large bile-ducts remain patent, and in which the gall-bladder is found to contain only uncoloured mucus, appear to be in reality obstructive. In such cases the obstruction must be located in the smaller bile-ducts

throughout the liver, and, whilst it is probably attributable in part to increased viscidity of the bile, in which, as a result of hæmolysis, the pigment is increased in amount, it is also ascribed, perhaps with still greater probability, to a catarrh of the smaller ducts set up by the poison at work. Evidences of such catarrh are met with.[5] Yet another theory must be mentioned—namely, that there is a direct passage of bile-pigment from the hepatic cells into the blood.[6]

It used to be believed that the presence in, or absence from the urine of bile-salts afforded evidence of the hæmatogenous or hepatogenous origin of jaundice in any particular case. When obstruction occurs, one would expect the resorption of bile-salts and pigments alike; whereas if the bile-pigment has been formed elsewhere than in the liver, no increase of bile-salts in the blood is to be expected. However, more recent investigation has deprived this distinction of all value, and the demonstration, by Stadelmann[7] and W. Hunter,[8] of bile-salts in the urine in a variety of jaundice so purely toxic as that which results when animals are poisoned with toluene-diamine supplies a powerful argument for the hepatogenous nature of such jaundice.

Bile-salts are often not to be detected in the urine in forms of jaundice which are undoubtedly obstructive, especially after the obstruction has existed for some days, and consequently their absence in any given case affords no valid evidence of hæmatogenous origin.

Why the bile-salts tend to disappear from the urine after jaundice is fairly established is not very easy to explain. It can hardly be that they are destroyed in the organism, in view of the established fact that when bile-salts are injected into the blood they are excreted as such. If they were deposited in the tissues, we should expect to find them in the urine also, as we do the bile-pigments, and there seems to be no escape from the conclusion that their formation is inhibited when jaundice exists. In cases of jaundice in which a biliary fistula has been established, the quantity of bile-salts in the fistula bile is markedly below the normal. This is doubtless in part due to their failure to enter the intestine, for it is certain that under normal conditions the bile-salts which enter the intestine are in part reabsorbed and re-excreted in the bile, just as when injected they are largely excreted by the same channel. However, an interference with this circulation of bile-salts will not explain all the observed facts, and fails to account for their scanty excretion in the urine in cases of jaundice in which the obstruction is not complete and some bile still enters the intestine. This much is clear: that the bile-salts, which possess conspicuous toxic properties, are not present in the blood of jaundiced patients in quantities sufficient to work any serious harm; and this is proved by the fact that, although these substances exert a strong hæmo-

lytic action, no evidence of active hæmolysis is obtained in cases of jaundice, with the exception of those in which a hæmolytic poison of another kind is itself the cause of the icterus.

As regards a third important constituent of the bile, cholesterin, there is no evidence that it undergoes absorption as the pigments and salts do, or that it plays any part at all in the causation of the symptoms which accompany jaundice. Even in the rare cases, which are not cases of jaundice, in which cholesterin crystals are found in abundance in the urine, the cholesterin is apparently not excreted from the blood by the kidneys. It would rather appear that it is a local product of a diseased urinary mucous membrane, or is formed in cavities communicating with the urinary tract. Cases of chronic cystitis and pyelitis, and of hydronephrosis, are among those in which cholesterinuria has most often been observed. It is, indeed, probable that, as Naunyn[9] holds, the cholesterin of the bile and of gall-stones is also a local product of the gall-bladder and biliary passages.

It is not yet possible to attribute all the symptoms which are wont to accompany jaundice to particular constituents of the resorbed bile. The pigments themselves have comparatively slight toxic properties, which are not manifested in jaundice; but to them the coloration of the skin and some excreta and secreta are undoubtedly due. The itching which is so common a symptom has been ascribed to them, but it may precede any obvious discoloration of the skin. Even the xanthopsia, which has naturally been set down to staining of the ocular media with bile-pigment, is by no means strictly proportional to the depth of the jaundice.

The bile-pigment is found in the blood-serum, in serous effusions, and in the sweat, as well as in the urine; from some excretions, such as saliva and tears, it is absent. In the urine its appearance usually anticipates pigmentation of the skin, and, after the obstruction has been removed, it disappears from the urine whilst the skin is still deeply tinted. At this period the urine is often rich in urobilin, but there is no adequate evidence that the skin is ever coloured by urobilin instead of bile-pigment—in other words, that a true urobilin-jaundice exists. In cases which might be supposed to have such a nature, bilirubin has been found in the blood and serous fluids. In those cases of slight persistent jaundice which are wont to occur in families, in which an icteric tint of the skin and conjunctivæ is constantly present, the urine is usually free from bile-pigment, and hence the name of "acholuric family jaundice" has been applied to the condition.

The colour of the skin varies. In cases of long-standing jaundice a dusky green tint develops, which is presumably due to oxidation of some of the deposited bilirubin to biliverdin, whereas the yellow tint of recent jaundice is undoubtedly due to bilirubin.

To the influence of resorbed bile-salts the slowing of the pulse

alone can be confidently ascribed, for such slowing of the beat is produced when these substances are introduced into the circulation.

**Effects of the Absence of Bile from the Intestine.**—In connection with the chemical pathology of jaundice, there must be taken into account not only the effects of the resorption of bile-constituents, but also those of the withholding of the bile from the intestine.

The characters of acholic stools are sufficiently familiar, but it must be pointed out that the fact that the stools have these characters is not in itself sufficient proof of the complete occlusion of the bile-ducts. Such stools are abnormally rich in fats, to the presence of which their pallor is largely due, and acholic fæces may contain considerable quantities of the chromogen of urobilin. The presence or absence of urobilin in them has been utilized by Riva and Zoja[10] as a test for the complete shutting off of the bile. When some fæcal material is extracted with chloroform, and a few drops of hydrochloric acid, containing a trace of nitric acid, are added, the characteristic absorption band of urobilin will be seen when the extract is examined with the spectroscope; whereas when there is complete biliary obstruction, no urobilin band appears, or more often a faint shadowy band is seen, which is probably due to the entrance of some bilirubin into the intestine from its jaundiced walls.

Our knowledge of the effects of the absence of bile from the intestine upon the absorption of the several classes of foodstuffs is chiefly derived from the researches of Friedrich Müller,[11] the results of which have been confirmed by A. Schmidt[12] and other more recent investigators.

In cases in which obstruction is complete, and no bile enters the intestine, the assimilation of carbohydrates is not appreciably impaired, nor is the utilization of proteins interfered with to any noticeable extent.

With fats the case is very different, for the withdrawal of the bile interferes seriously with their utilization. The acholic stools of jaundiced patients owe their whiteness largely to the abundance of fats which they contain. Whereas the withdrawal of the pancreatic juice from the intestine leads, as a rule, to the passage of stools rich in neutral fats, and, if a diet rich in fat be taken, to the escape from the anus of oil which solidifies on cooling; in cases of biliary obstruction the stools, although very fatty, contain neutral fats, fatty acids, and soaps in the normal proportions. It is the absorption and not the splitting of the fats that is impaired. When examined under the microscope, acholic stools are found to contain large numbers of acicular crystals, which were at one time supposed to be crystals of tyrosin, but which are now known to consist of calcium and magnesium soaps.

The peculiar and offensive odour of acholic stools has been ascribed to the loss of the antiseptic influence of bile. However, there is some doubt whether the bile possesses any conspicuous

power of restraining bacterial growth. Bile itself readily undergoes bacterial decomposition, and estimations of the aromatic sulphates in the urine of jaundiced patients have yielded conflicting results, which are perhaps due to the fact that biliary obstruction may have its origin in very different morbid processes. It may be that the bacterial decomposition, to which the offensive odour of the stools is due, is rather to be ascribed to the loss of the laxative action of the hepatic secretion, and consequent stagnation of the intestinal contents.

2. **Gall-Stones.**—It will be most convenient to consider in this place the formation of concretions in the gall-bladder and biliary passages, which is so common a pathological event, and which is capable of giving rise to a variety of morbid consequences.

Gall-stones are of many varieties, which it is not necessary to describe here; but those met with in human subjects are made up of two main constituents—namely, cholesterin and the calcium compound of bilirubin. In some of the lower animals, such as oxen, large calculi, composed almost entirely of bilirubin-calcium, are not uncommon, but in human beings such stones rarely attain to any great dimensions. In addition to bilirubin, other pigments, such as biliverdin and bilifuscin, enter into the composition of calculi. Stones largely composed of inorganic materials, such as calcium carbonate and calcium phosphate, rarely occur in human subjects.

Cholesterin is a constituent of normal bile, to the amount of about 2 per cent.; but, as has been mentioned already, there is no reason for believing that it is a specific secretion of the liver, or that, although it is present in blood-corpuscles and in the plasma, it is excreted by the liver from the blood. It is found in all secretions of mucous membranes, and in special abundance when these are the seats of chronic inflammatory processes. In the bile it is held in solution by the influence of the bile-salts.

As the outcome of his investigations, Naunyn[13] arrived at the conclusion that the cholesterin of the bile is derived from the mucous membrane of the gall-bladder and biliary passages. The calcium which enters into combination with bilirubin, and in so doing takes no unimportant share in the formation of biliary calculi, probably has a similar origin, for Jankau[14] showed that the feeding of animals with cholesterin does not increase the quantity in the bile, and that, speaking generally, there is no increase of lime in the bile when calcium salts are added to the food. Hence it would seem that the conditions most favourable to the formation of gall-stones are probably produced by morbid conditions of the biliary passages—a "calculous-forming catarrh," as Naunyn names it. There are good grounds for the belief that such catarrh is set up by an infection of the gall-bladder and ducts, and, further, that the *Bacillus coli communis* is the infective agent. Such bacterial invasion is presumably favoured by stagnation of bile in

the gall-bladder, stagnation which may have its origin in various conditions, such as sagging of the gall-bladder.

Naunyn and Labes[15] have shown, by experiments upon animals, that, in the absence of such a catarrhal condition, the mere introduction of foreign bodies, and even of gall-stones, into the gall-bladder does not in itself suffice to start calculus formation around the foreign bodies.

Gall-stones are usually laminated, and, although some laminæ are much more deeply pigmented than others, these darker layers contain much cholesterin as well as pigment. When a section is made of an ordinary faceted calculus from the gall-bladder, it is seen that the laminæ follow the contour of the facets. From this it is evident that the forms of such calculi are due to moulding by mutual pressure whilst they are still soft. Were the facets due to attrition of one stone against another, the successive laminæ would of necessity be cut across, which is not the case. Since, then, all the calculi of such a collection are in a soft state at the same moment, there is no escape from the conclusion that they are formed simultaneously, presumably as the result of a temporary catarrhal inflammation, and not one after another in the course of a chronic morbid process.

Naunyn has further shown that gall-stones are apt to undergo conspicuous changes during a prolonged sojourn in the gall-bladder, and that a molecular rearrangement takes place in them, which results in the formation of crystals of cholesterin, and the extrusion of the bilirubin calcium which they originally contained. He also believes that fresh cholesterin permeates into the calculi through infiltration channels, such as are familar to students of mineralogy. In this manner a stone which was originally of mixed composition may become converted into a brilliantly white cholesterin calculus, which exhibits a radiating crystalline structure throughout and is studded upon its surface with crystalline excrescences.

3. **The Liver and the Urinary Pigments.**—There is good reason to believe that the metabolic changes which result in the formation of some at least of the pigments met with in the urine are carried out in the liver, and disease of that organ undoubtedly has a conspicuous influence upon the amounts of such pigments excreted.

Of the place of formation of the principal urinary colouring matter, and of the conditions which control the excretion of urochrome, practically nothing is as yet known,[16] although it is probable that the quantities of this pigment present in the urine vary widely in disease, as is the case with the other pigments. It evidently is not formed from bilirubin in the intestine, seeing that its formation is not appreciably interfered with when the common bile-duct is completely occluded. It is present in small amounts in the completely acholic stools, when such obstruction exists, just as it is in normal fæcal material. Nor is any evidence

as yet forthcoming which points to the liver as the seat of its formation, nor to any conspicuous influence of hepatic disease upon its excretion in the urine.

With uroerythrin, the pigment which so often imparts a pink colour to uratic sediments, the case is wholly different. Clinical observation suffices to show that its excretion is profoundly influenced by the condition of the liver. From strictly normal urine it is probably wholly absent, but very trifling derangements certainly suffice to cause it to appear. On the other hand, no clinical fact can be more easily verified than that the deposition of urate sediments, deeply tinted with uroerythrin, is usually met with in the urine of patients suffering from hepatic disease or disorder of some kind. The liver may be the seat of organic disease, such as cirrhosis or carcinoma, or of passive congestion, such as results from cardiac derangements, or may be affected by toxic influences, as in some febrile maladies, and probably in gout also. Riva[17] quotes the instance of a colleague who usually took no alcohol, in whose case a glass or two of wine sufficed to cause an excretion of this pigment, and experience teaches that very slight alimentary derangements may bring about such a result; but, although it is probable that the hepatic functions are implicated in such cases, we are not justified in asserting positively that apart from derangements of the liver there is no excretion of uroerythrin in the urine.

Although its properties have been studied in some detail by several observers, and although, indeed, it was the first of the urinary colouring matters to receive special study, the nature and source of this highly unstable pigment remain unknown. It cannot be assigned a place in any of the recognized groups of animal colouring matters. Its properties, spectroscopic and other, lend no countenance to the idea that it is a derivative of hæmoglobin. It is obviously not a melanin, and it bears no resemblance to the tryptophane derivatives. It is least unlike the lipochromes.

Even when no uratic sediment is deposited, the presence of abundance of uroerythrin may be recognized by the fiery orange colour which it imparts to the urine, and which is changed to a much paler greenish tint by alkalies.

Of hæmatoporphyrin our knowledge is much more complete, and its position as a derivative of hæmoglobin admits of no doubt. It is true that pigments closely resembling, if not identical with, hæmatoporphyrin in their spectroscopic properties may be obtained from other parent substances, such as chlorophyll and turacin; but although Stokvis[18] was inclined to think that it might be derived from the chlorophyll of vegetable foods, there are no sufficient grounds for supposing that the hæmatoporphyrin of the urine is derived from any other source than hæmoglobin.

Nencki and Sieber[19] suggested that hæmatoporphyrin might represent a stage in the building up of hæmoglobin, but the principal

evidence adduced—viz., the imperfect excretion of the pigment when it is injected subcutaneously into dogs—is greatly weakened by the observation of Otto Neubauer, that much of the pigment so injected is excreted in the bile.

Hæmatoporphyrin is evidently a product of normal metabolism, for it may be found in traces in all normal urines, provided that a sufficiently delicate method is employed and sufficient quantities of urine are taken. It also occurs in traces in the fæces and in the bile, and is present in considerable larger amount in meconium. That the traces present in fæces are not merely derived from the bile is demonstrated by the fact that they are still present even when the common bile-duct is completely occluded.

It may be that the traces of hæmatoporphyrin normally excreted represent a by-product of the process of bilirubin formation. It must be remembered that the quantities are very minute, and, but for the fact that the spectra of this pigment are so conspicuous and distinctive, might well defy detection by ordinary chemical methods unless very large quantities of material were dealt with.

The study of the numerous cases in which hæmatoporphyrin appears in the urine in quantities considerably larger than the normal traces, but still insufficient to exert any obvious influence upon its tint, leads to the conclusion that the condition of the liver is the main determining factor in such increased excretion. Abnormal hæmolysis has no obvious effect upon the output. In pernicious anæmia hæmatoporphyrinuria is not a symptom, and even in cases of conspicuous hæmatoporphyrinuria, such as results from chronic sulphonal-poisoning, blood-counts afford no evidence of concurrent hæmolysis. The number of red corpuscles may be low in any particular case, but it is not necessarily so. The association of increased output of this pigment with hepatic disease has been noticed by several independent observers, and it is especially in connection with diseases which produce diffuse changes throughout the hepatic substance, such as cirrhosis, fatty degeneration, leukæmia, and valvular heart disease with passive congestion of the liver, that a somewhat increased excretion of hæmatoporphyrin is usually observed.

The increased excretion which is, as Stokvis showed, so constant a feature of chronic lead-poisoning may be attributable to the fatty degeneration of the liver which lead induces. In fevers, and especially in rheumatic fever, as well as in gout, slight degrees of hæmatoporphyrinuria are commonly observed. The cloudy swelling found post mortem bears witness to the effect of febrile conditions upon the hepatic parenchyma, and in gout hepatic lesions of slight degree are by no means uncommon. In connection with these latter diseases, the evidence supplied by uroerythrin points in the same direction.

How far the pronounced hæmatoporphyrinuria, with the excretion of dark red, or even black, urine, which usually follows the taking

of sulphonal, but which is occasionally met with apart from sulphonal-poisoning, is attributable to hepatic lesions cannot be decided on the evidence available. The conspicuous fatty and other degenerative changes which have been found post mortem in some of the sulphonal cases renders it probable that the drug in question exerts a severe toxic action upon the hepatic parenchyma. In the cases in which sulphonal has no part, the hæmatoporphyrinuria appears to have no such grave import. It has been associated with a variety of morbid conditions, such as hydroa æstivale, gastric ulcer with hæmatemesis, and phthisis pulmonalis; and in one case, recorded by Nebelthau, the symptom had existed as long as the patient, who was a victim of congenital syphilis, could remember. It may be mentioned that, although such urines contain considerable amounts of hæmatoporphyrin, their colour is mainly due to other abnormal pigments, of which little is at present known.

Of special interest are the cases in which hæmatoporphyrinuria is associated with hydroa æstivale. They appear to constitute a distinct group for which Hans Güntner,[20] who has made a very careful study of the condition, proposes the name of "congenital hæmatoporphyria." The urinary anomaly and the summer eruption, which latter is a manifestation of an abnormal sensitiveness of the skin to light as distinguished from heat, usually date from early childhood, and as the patient gets older the eruption brings about a destruction of tissue of the nose, ears, cheeks and fingers, which suggests a diagnosis of leprosy, pellagra or syringomyelia. The original and classical case of hæmatoporphyrinuria, described by Baumstark and Schulz, was of this kind. In it conspicuous pigmentation of the bones of the skull was found after the patient's death.

The question of the relation of the excretion of urobilin to liver disease has been much discussed, and is surrounded by difficulties. Under normal conditions the fæces are rich in urobilin and its chromogen, whereas the quantities contained in the urine are very minute. Both in their spectroscopic and other properties, and in their ultimate composition, the urobilin of fæces is identical with that of the urine.[21]

Although some urobilin is found in the bile, there can be no doubt that the bulk of that which is contained in the fæces is formed in the intestine. It may be taken as proved that it is formed from the bile-pigment, and there is little doubt that the conversion is brought about by the agency of the intestinal bacteria. Pigments having the main properties of urobilin have been obtained, in various ways, from bilirubin, hæmatin and hæmatoporphyrin. Of these the hydrobilirubin which Maly got by the reduction of bilirubin with sodium amalgam has received most attention.

Hopkins and Garrod, who made a series of analyses of urobilin extracted both from urine and fæces, found that their products

contained some 4 per cent. of nitrogen, less than half the quantity present in hydrobilirubin. On the other hand, Hans Fischer,[21] in a more recent research, has succeeded in obtaining the same chromogen of urobilin, in crystalline form, both by reduction of bilirubin and by extraction from urine. Hence he concludes that, when pure, Maly's product and natural urobilin are identical, and that the previous analyses of both hydrobilirubin and urobilin were made upon impure products.

There is, indeed, much evidence to show that the urobilin of urine has been absorbed from the bowel. When, for any reason, the formation of the fæcal pigment is arrested, urobilin tends to disappear from the urine also. This is the case, as Riva[22] showed, in acute yellow atrophy of the liver and in phosphorus-poisoning, and also in cases of typhoid fever in which acid stools, deeply stained with biliverdin, are passed. Still more conclusive are the effects of complete obstruction of the bile-ducts, and Friedrich Müller[23] found that, when pig's bile was administered by a tube to a patient with complete biliary obstruction, whose fæces and urine were alike urobilin-free, urobilin reappeared both in the solid and liquid excreta. That the intestine is the main seat of urobilin formation admits of no doubt, and it is merely in question whether it is the only seat of the process.

In support of the view that urobilin may have its origin elsewhere, much stress has been laid upon a most interesting observation of D. Gerhardt,[24] of a patient whose bile-duct was found *post mortem* to be completely occluded by carcinomatous growth, and whose fæces contained no urobilin, or mere traces thereof. There was a hæmorrhagic ascites, and the urine contained a quantity of urobilin. Hildebrandt considers that the evidence supplied by this case is invalidated by the fact, stated by Gerhardt, that the fæces were not more completely free from pigment than is usually the case in complete biliary occlusion; but this hardly appears to get over the difficulty, seeing that in such circumstances traces of urobilin are almost always to be detected in the fæces, and are probably formed from bile-pigment derived from the jaundiced intestinal walls.

The controversy on the question whether urobilinuria is or is not always due to absorption from the intestine is not yet laid to rest, but it appears to the writer that, in spite of Gerhardt's case, the bulk of evidence is strongly in favour of the intestinal theory. Of recent years the protagonists have been Hildebrandt,[25] who maintains the intestinal theory, and Fischler,[26] who advocates the hæmatogenous origin of the pigment.

Unquestionably, disease of the liver has conspicuous influence upon the formation of urobilin, and this organ has been regarded by Hayem, Tessier, and others, as the main seat of the process. The explanation of the known facts presents undoubted difficulties

on the intestinal theory. These facts are of two kinds. In many cases of jaundice removal of the biliary obstruction is followed by a conspicuous urobilinuria, whereas bile-pigment ceases to be excreted in the urine. This observation is probably the origin of the theory of "urobilin jaundice," and it is not difficult to explain it if we suppose that the entry into the intestine of an accumulation of pent-up bile is followed by an unusually abundant formation of urobilin. However, in some cases in which the bile-ducts are only partially obstructed, and diminished quantities of bile are entering the intestine, urobilinuria is nevertheless observed. Vaughan Harley[27] suggested that this might be due to partial withdrawal of the antiseptic action of the bile, and consequent increase of bacterial activity in the intestine.

The facts of the second group present much greater difficulties. Thus, in diseases of the liver, such as cirrhosis, which cause but little biliary obstruction, the excretion of urobilin is often far greater than the normal, and in order to explain this fact, modifications of the purely intestinal theory—the so-called "hepato-intestinal theories"—have been advanced. The two most important of such theories place the intervention of the liver at the beginning and end of the urobilin cycle respectively.

Riva and Zoja[28] believe that the yield of urobilin and its chromogen in the intestine is largely dependent upon the quality as well as the quantity of the bile. Their observations lead them to conclude that, under the influence of the intestinal bacteria, reddish-brown bile yields urobilin much more readily than bile which has a greenish colour—in other words, that the readiness with which urobilin is formed depends upon the relative proportions of bilirubin and biliverdin in the bile. Obviously, if this view be correct, other derivatives of bile-pigment besides urobilin must be formed in the intestine, as otherwise that portion of the bile-pigment which escapes conversion into urobilin would be found in the fæces unchanged, which is not the case. This supposition is almost certainly justified, seeing that the extraction of as much as possible of the urobilin and urobilogen from fæcal material has but little effect upon its colour.

An alternative theory, put forward by Murri[29] and Beck,[30] supposes that the influence of the liver is exerted after the pigment has been absorbed from the bowel, and that the absorbed urobilin is to a large extent intercepted by the liver, and re-enters the intestine with the bile. It has been shown that under ordinary conditions urobilin disappears from the bile, as well as from the fæces, when the bile-ducts are completely obstructed. Vatili[31] has even maintained, but upon evidence which cannot be regarded as conclusive, that the absorbed urobilin is in part reconverted into bilirubin by the liver.

The very scanty presence of urobilin in normal urine, as com-

pared with its abundant presence in the fæces, and the difficulty of establishing any definite parallelism between the quantities in fæces and urine respectively, suggest that little of the absorbed pigment reaches the kidneys unchanged; but Riva objects to Murri's theory that, in cases of cirrhosis and carcinoma hepatis, the fæcal as well as the urinary urobilin is conspicuously increased in quantity.

The increased excretion of urobilin in cases in which extravasated blood is undergoing absorption, and the frequent presence of abundance of this pigment in the urine in cases of pernicious anæmia, which was first observed by Mott[32] and W. Hunter[33] and has been utilized as a diagnostic sign of hæmolytic anæmia, point to a close connection between urobilinuria and the breaking down of hæmoglobin. If the intestinal theory be correct, it must be supposed that a pleiochromia of the bile affords an extra supply of bile-pigment to be converted in the intestine.

Another urinary pigment which calls for mention in connection with hepatic disease is melanin.[34] The excretion of this substance, or, rather, of its chromogen melanogen, is well recognized as an important diagnostic sign of melanotic sarcoma. The statement met with in so many books, that melanuria occurs in connection with other, and especially with marasmic, conditions cannot be accepted upon the recorded evidence. The writer has met with no case in which the urine yielded the characteristic reactions of melanuria—viz., blackening with ferric chloride, the reaction with bromine-water, and the Prussian blue nitroprusside reaction—except cases of generalized melanotic sarcoma; and reference to the cases repeatedly quoted in support of the above statement shows that they were recorded before these reactions were known. Moreover, it is usually mentioned that the urines in question were rich in indican, and the published descriptions are quite compatible with the view that they were cases in which indol derivatives were excreted in unusual abundance. Such indican urines are often brown in tint, darken conspicuously on standing, and blacken when warmed with nitric acid. These changes are not due to indoxyl sulphate, but to higher oxidation products of indol which accompany it.

In cases of melanotic sarcoma, melanuria is by no means a constant symptom. It is not observed as long as the growth is confined to its primary seat. Melanuria bears witness to invasion of the internal organs, and its degree will be found to be proportionate to the extent to which the liver has been invaded, and its substance has been replaced by the melanotic growth. When, as is sometimes the case, the hepatic growths are but slightly pigmented the quantity of melanin in the urine is correspondingly less. Invasion of the kidneys does not appear to have any influence in determining melanuria, but these organs are sometimes stained by the pigment in its passage.[35]

**The Influence of Hepatic Disease upon Protein Metabolism.**—Observations bearing upon the effects of disease of the liver upon protein metabolism have been for the most part carried out in cases of acute yellow atrophy and of cirrhosis. These two morbid conditions produce widespread destructive changes in the hepatic parenchyma, although these changes are of very different kinds in the one and in the other. As regards cirrhosis, it must be remembered that the lesions classed under that heading are by no means uniform in character, and it is therefore not surprising that the results obtained differ rather widely in different cases. Nor must it be forgotten that any at all complete suspension of the functional activity of the parenchyma of the organ is not compatible with the prolongation of life beyond a very short period.

**Urea.**—Although, in the light of more recent researches, the liver cannot be regarded as the only seat of urea formation, there can be no doubt that it is an important seat of the process, and is capable of forming urea synthetically from ammonium salts conveyed to it by the portal vein. It would therefore not be surprising if this synthesis were interfered with to some extent by hepatic disease. As a matter of fact, in some cases of grave disease of the hepatic parenchyma the output of urea in the urine is greatly diminished, and the percentage of urea nitrogen may fall as low as 50 to 60. At the same time there is a conspicuously increased excretion of ammonia. However, even in cases of acute yellow atrophy which terminate fatally, there may be, as Richter[36] and others have shown, no obvious diminution of urea in the urine, and no very marked excess of ammonia. In cirrhosis hepatis, as might be expected from the less extensive destruction of the parenchyma of the liver, the diminution of the urea output is less conspicuous, but an increased excretion of ammonia is not unfrequently observed.

We are not justified in assuming that these phenomena, when present, are necessarily due to failure of the liver to effect the conversion of ammonia into urea owing to impairment of its synthetic power, for it is a well-recognized fact that the same results may be brought about by the action of a wholly different cause. The interception of ammonia, and its employment to neutralize excess of acids, whether absorbed from the alimentary canal or formed within the body, is one of the most important of the protective mechanisms against chemical poisons. The ammonia so utilized is withdrawn from the ordinary paths of metabolism, and a diminished formation of urea follows as a consequence of this withdrawal. Hence it is possible that in hepatic disease, as the result of metabolic derangements, an excess of acid or acids may be produced which the ammonia is required to neutralize, and that the observed phenomena are in reality due to an acidosis, such as is seen in diabetic coma, and is now generally held to be the actual cause of such coma.

The results of some experiments which have been carried out on animals have important bearings upon this question. Thus, when an Eck's fistula is established in a dog, and the portal blood is caused to flow directly into the inferior vena cava instead of traversing the portal capillaries in the liver, the animal succumbs to toxic influences after a period which is shorter or longer according as the food which it takes is rich or poor in proteins. The output of urea is diminished, whereas the ammonia excreted is greatly increased in amount, and the urine becomes alkaline. Seeing that the excess of ammonia excreted more than suffices for the neutralization of all acids present, it is obvious that its presence is not due to acidosis, but must rather be attributed to the failure of the ammonia in the portal blood to become converted into urea. We may indeed conclude that, as Salaskin and Zaleski[37] hold, the animal succumbs to poisoning by ammonia, or more probably by ammonium carbamate, the halfway substance between ammonium carbonate and urea.

When, on the other hand, the liver of a dog is removed as completely as possible, the toxic picture presented in the hours during which the animal survives is a wholly different one, as was demonstrated by Salaskin and Zaleski. The urine, instead of being alkaline, becomes strongly acid, and the death of the animal is to be ascribed to acid-poisoning. The actual nature of the acids concerned is not fully made out. Lactic acid is certainly one of them, but the observers referred to believe that intermediate products of protein metabolism of high molecular weight share in bringing about the fatal result.

Münzer,[38] as the outcome of a series of observations upon cases of phosphorus-poisoning, arrived at the conclusion that in such cases the increased excretion of ammonia which is observed is due to an acidosis in which sarco-lactic acid plays an important part. As in acidosis of other kinds, the carbon dioxide of the blocd was, in the cases observed, diminished in quantity, presumably owing to the reduced carrying-power of blood poor in sodium bicarbonate. Münzer found that the output of ammonia was diminished by the administration of sodium bicarbonate, and he further showed that in rabbits—in which animals, as in other vegetivora, the protective neutralization of acids by ammonia is not observed—poisoning by phosphorus fails to induce the increased excretion of ammonia which results in carnivorous animals.

Such an effect upon the excretion of ammonia of giving sodium bicarbonate by the mouth, has usually been accepted as affording conclusive evidence that the excess of ammonia is due to acidosis, and that the supply of fixed alkali obviates to some extent the necessity for calling upon ammonia to neutralize the acid poison. It must be mentioned, however, that Pflaunder,[39] who has specially investigated the acidosis of suckling infants, throws some doubt

upon the conclusive character of such evidence. He suggests that urine rendered alkaline by fixed alkalies is much less capable of retaining ammonia in the form of stable salts than urine which has an acid reaction, and, further, that increased alkalinity of the blood may possibly stimulate the metabolic processes, and among these the process of urea formation. It may be objected to the second of these suggestions that it is conjectural, and to the first that in diabetes the reduction of the output of ammonia when sodium carbonate is given commences long before the urine is rendered alkaline.

If the power of the liver to form urea from the ammonia conveyed to it is impaired as a consequence of disease, we should expect that, when ammonium carbonate is given by the mouth, to a patient suffering from hepatic disease, the excretion of ammonia would be thereby increased, whereas that of urea would not to any conspicuous extent. Weintraud[40] found that, in cases of cirrhosis hepatis, ammonium carbonate given by the mouth was excreted as urea, thus supplying a strong argument in support of the acidosis theory; but Chabrese[41] obtained only a slight increase of the urea excretion, or none at all, in cases of the same disease, and the results obtained by other investigators have been far from uniform. Here, however, the wide differences in character among cases of cirrhosis of the liver must be taken into account. Turning to evidence of a more positive kind, it is certain that an abnormal formation of acids is a common phenomenon in hepatic diseases. Among the acids formed in excess sarco-lactic acid stands conspicuous; volatile fatty acids are also produced, as von Jaksch[42] has shown, and acids of the aromatic group, such as oxymandelic acid, which is presumably a derivative of tyrosin, and was first detected in the urine of patients with acute yellow atrophy by Schultzen and Reiss, and oxyparacumaric acid found by Röhmann.[43]

It is clear, then, that there is very strong evidence that the diminished excretion of urea and increased excretion of ammonia which accompanies hepatic disease is due to acidosis rather than to a diminution of the power of the liver to form urea; but in the present state of our knowledge the question cannot be regarded as finally settled.

**Leucin and Tyrosin.**—Peculiar interest attaches to the presence of leucin and tyrosin in the urine in some forms of hepatic disease in which the destruction of the parenchyma of the liver is very pronounced. Their occurrence was first observed by Frerichs,[44] in a case of acute yellow atrophy, and Schultzen and Reiss detected quantities up to 1·5 grammes in the urine of twenty-four hours in such cases. In association with no other hepatic lesion are they so frequently or so abundantly present. In phosphorus-poisoning the urine may contain these amino-acids, but less often and in smaller amounts, and Dixon Mann[45] has found them in cases

of hepatic congestion due to cardiac disease. In cases of cirrhosis hepatis they have been sought for in vain by von Noorden and by Stadelmann,[46] but Greco has described crystals of leucin in the urine of sufferers from this malady.[47] In cases of acute yellow atrophy, leucin and tyrosin have been abundantly present in the liver itself, and also in the blood; and in one case Carl Neuberg and P. F. Richter[48] extracted as much as 0·787 gramme of tyrosin, 1·102 grammes of leucin, and 0·24 gramme of lysin, from 345 c.c. of blood collected *post mortem*. Calculating the total blood at 4 to 5 kilogrammes, this implies a total content of no less than 30 grammes of free amino-acids; but in the case in question there was an acute nephritis, the quantities in the urine were comparatively small, and retention may have brought about an accumulation in the blood.

Except in the above-mentioned grave hepatic diseases, the presence of leucin and tyrosin in the urine has seldom been conclusively demonstrated. In pernicious anæmia these substances have been occasionally found by Laache[49] and von Noorden.[50] Walter Smith[51] has described an abundant sediment of leucin in the urine of a young woman who had no serious illness. The presence of these amino-acids in the urine in cystinuria will be referred to in connection with that anomaly of protein metabolism.

The view was formerly held that the appearance of leucin and tyrosin in the urine in cases of grave hepatic disease is due to an inability or diminished ability of the diseased organ to break them down further. However, the fact, which was demonstrated by P. F. Richter,[52] that they may occur in the urine in cases of acute yellow atrophy in which there is no marked impairment of urea formation and no conspicuous increase of the excreted ammonia, is opposed to such an explanation. Von Noorden suggested that in acute yellow atrophy leucin and tyrosin might be formed in the tissues as a result of bacterial action, whereas the comparatively small amounts excreted in some cases of phosphorus-poisoning might be derived from the intestine. Impaired destructive power of the liver might be regarded as a contributing factor in both conditions.

Since Jacobi[53] showed that leucin and tyrosin are formed abundantly in autolysis of the liver under sterile conditions, it has come to be a very general opinion that their presence in the blood, urine, and liver itself, in cases of acute yellow atrophy and phosphorus-poisoning, is due to the breaking down of the parenchyma of the liver—*autolysis intra vitam*. That in both conditions the hepatic parenchyma undergoes extensive destruction admits of no question, but the observations of Neuberg and Richter,[54] referred to above, on a case of acute yellow atrophy, suggest that such destruction cannot be alone responsible for the production of such large quantities of amino-acids as were present in the blood. As these observers point out, the breaking down of the whole of the

liver substance—a result which is, of course, never attained—would not suffice to account for the yield.

**Purin Substances.**—Minkowski,[55] in his experiments on geese from which the liver had been removed, observed an enormous diminution of the excretion of uric acid. The uric acid nitrogen fell from the normal 60 to 70 per cent. of the total nitrogen output to as low a figure as 3 to 6 per cent. However, the part played by uric acid in the nitrogenous excretion of birds is so far out of proportion to that which it plays in mammals, that it can hardly be doubted that in birds the chief mode of its formation is entirely different. Nuclein breakdown must be wholly inadequate to account for the quantities of uric acid excreted. It is therefore not surprising to find that in man even the gravest of hepatic diseases, acute yellow atrophy, has little or no effect in diminishing the excretion of uric acid. Indeed, observations by Richter,[56] Münzer,[57] Kaufmann, and Mohr,[58] and Rem-Picci,[59] have revealed an actual increase of the total output of purin substances. Weintraud[60] also found that in acute yellow atrophy thymus feeding was followed by the usual increase of uric acid in the urine.

**Creatin and Creatinin.**—Some recent investigations by E. Mellanby on the excretion of creatin and creatinin afford indications of a profound influence of diseases of the liver upon the metabolism of these substances. Mellanby[61] estimated the creatinin and creatin in the urine of a small number of patients suffering from cirrhosis hepatis, venous engorgement of the liver due to mitral stenosis, and carcinoma of that organ. In the cases of the two former groups the daily output of creatinin was conspicuously diminished, below the normal excretion of one or two grammes; in the carcinoma cases, two in number, there was not only a like diminution of creatinin, but also creatin itself was present in the urine in considerable quantity, amounting in one instance to as much as 1·5 grammes in the urine of twenty-four hours. Both patients with carcinoma had wasted greatly, and Mellanby is inclined to attribute the observed phenomena to the liberation of creatin as the result of the breaking down of the wasted muscles, and its excretion without further change.

**Formation of Acetone from Protein Fractions.**—G. Embden, Saloman, and F. Schmidt,[62] have shown that, when certain of the protein fractions are perfused through the liver, acetone is formed, whereas others yield no such product. The fractions in question are tyrosin, phenyl-alanin, and leucin. Baer and Blum[63] have further shown that these same substances, when administered to a diabetic, cause an increased excretion of $\beta$-oxybutyric acid. Hence it seems clear that proteins as well as fats must play important parts in the formation of the bodies of the acetone group

in diabetes and other morbid conditions, and that the liver is the seat of the changes of this class.

**Protein Metabolism in General.**—The metabolism of proteins as a whole shows no constant disturbance as a result of hepatic disease. In destructive maladies, such as acute yellow atrophy, there is evidence of increased destruction of proteins in the organism. In cases of cirrhosis, as is inevitable, the accumulation of a bulky serous exudate, rich in albumin, in the peritoneal cavity modifies the nitrogenous equilibrium, by withdrawing protein from the ordinary paths of metabolism, and storage of nitrogen results; whereas during the period of absorption of ascitic exudates a correspondingly increased protein breakdown is observed.

Seeing how profoundly the appetite is wont to be affected in cases of hepatic disease, it is obvious that only such estimations of the nitrogenous output as are accompanied by determinations of the intake with the food are of any value for the study of the effects of such disease upon protein metabolism as a whole.

**The Effects of Hepatic Disease upon Carbohydrate Metabolism.**—As evidence of the important part which is played by the liver in connection with the metabolism of carbohydrates, it is only necessary to refer to the phenomenon of glycogen storage, of which it is an important, but not the only, seat. Moreover, it is a well-established fact that the storage of glycogen in the liver is much impaired by hepatic derangements. Even obstruction of the bile-ducts causes partial or complete disappearance of glycogen from the liver, as various experimenters have demonstrated. Thus, Wickham Legg[64] found that, in animals, after ligature of the common bile-duct the diabetic puncture no longer caused glycosuria, and his observations have been confirmed by others,[65] who have shown that under such conditions the liver is glycogen-free. Very conclusive in this connection are the observations of Dastre and Arthus,[66] who demonstrated that, when individual branches of the hepatic duct were ligatured, the corresponding areas of the liver were poorer in glycogen than the remainder of the gland.

There is no reason to doubt that in human beings who are subjects of obstructive jaundice a similar depletion of the hepatic glycogen occurs, and some positive evidence is supplied by an observation of von Noorden, who was unable to detect glycogen by microscopic examination in a fragment of liver which was brought away in an exploratory puncture in the case of a deeply jaundiced patient who was thought to have an hepatic abscess. Yet it would seem that the suspension of glycogen storage in the liver is no very serious matter for the organism, and that the function of the liver in this respect is sufficiently replaced by storage in the muscles. At least it may safely be asserted that disease of the liver as such has little tendency to cause glycosuria.

That glycosuria is a not uncommon accompaniment of cholelithiasis has been stated by several observers. Thus, Exner,[67] who examined the urine of forty patients with gall-stones before and after operation, found evidence of the presence of sugar in small amounts in all the cases but one. After operation the sugar diminished and disappeared in the course of three or four weeks. Gans,[68] too, had previously found sugar in the urine during and immediately after gall-stone attacks. On the other hand, Naunyn[69] failed to detect glycosuria in any case out of a series of 250; and Kausch,[70] who submits Exner's methods to a searching criticism, met with sugar in the urine in one only of fifteen cases of cholelithiasis. Zinn,[71] too, regards the excretion of sugar as a very uncommon event in this disease.

In cirrhosis hepatis, glycosuria is only exceptionally met with, although its occasional occurrence is not open to doubt. In some such cases there may be an association of cirrhosis with true diabetes, but it appears reasonable to suppose that the concurrence of glycosuria, or of its minor manifestation, alimentary glycosuria *ex amylo*, with cholelithiasis and with cirrhosis usually results from an extension of disease to the pancreas, such as is well known to occur. In a well-known case of cirrhosis, recorded by Quincke,[72] in which sugar was excreted, the presence of consecutive changes in other organs is specially mentioned in the report.

There is strong evidence that glycosuria is a not uncommon symptom in acute phosphorus-poisoning, as was first pointed out by Bollinger.[73] Cases illustrating this point have also been recorded by Huber, Reichel, and Laub.[74] The glycosuria appears on the third or fourth day, is transitory, and persists only for two or three days. In one of Laub's cases the sugar excreted in the urine amounted to 0·67 per cent.

Von Jaksch[75] has observed alimentary glycosuria at certain stages in cases of phosphorus-poisoning, and in a case of acute yellow atrophy. The occurrence of spontaneous glycosuria in acute yellow atrophy is not wholly unknown, for individual cases have been recorded by Tcherinoff in 1869, and by Soetbeer[76] in 1903. The interval of thirty-four years bears witness to its extreme rarity. There is little evidence that, in cases of liver disease in general, alimentary glycosuria, following the administration of dextrose in quantities insufficient to cause excretion of sugar by healthy persons, is at all a common phenomenon; but the recent researches of H. Strauss,[77] whose results have been abundantly confirmed by other observers,[78] have brought to light the very interesting fact that in patients whose livers are the seats of disease the power of dealing with lævulose is markedly impaired.

Sachs, working at Strauss's instigation, found that frogs deprived of their livers had less tolerance for lævulose than for dextrose and other sugars. Strauss accordingly investigated the effects of

the administration of lævulose to twenty-nine patients with hepatic diseases of various kinds, and to fifty-eight others who showed no signs of such disease. Of the twenty-nine patients, twenty-six (a ratio of 90 per cent.) were found to have alimentary lævulosuria; whereas of the fifty-nine patients of the second series, six only (a ratio of 10 per cent.) exhibited this peculiarity. In some of these latter cases there may have been latent hepatic trouble, such as chronic congestion with mitral stenosis, and the three negative cases in the hepatic series could be partly explained away.

Strauss suggests that, whereas glycogen storage from dextrose feeding may take place elsewhere than in the liver, such storage after lævulose feeding does not.

E. Sehrt,[79] who experimented upon the glycolytic actions of powders prepared from certain organs, including liver, pancreas, salivary glands, thyroid, and adrenals, found that none of the organs in question, with the exception of the pancreas, had in themselves the power of destroying glucose. The pancreas possessed this power, and a mixture of pancreas with muscle was specially potent. This same mixture had a similar destructive action upon galactose and dextro-rotatory arabinose, whereas against lævulose it was absolutely inert. On the other hand, liver and salivary gland exercised a slight but constant destructive action upon this sugar.

Whatever be the explanation of the phenomenon, that relative intolerance for lævulose is a symptom of hepatic disease may be regarded as an established fact, and this test may prove to be a very valuable clinical aid in cases in which the integrity of the liver is called in question, but in which the physical signs of hepatic disease are uncertain or absent.

**The Protective Functions of the Liver.**—Among the many functions which the liver performs, some of the most important are those which are concerned with the protection of the organism against poisons derived from the alimentary canal and carried to the liver by the portal circulation. That the gland exercises a protective power against inorganic poisons, such as mercury and arsenic, and also against members of the group of alkaloids, such as strychnine and atropine, does not appear to be open to doubt. There is also evidence that the liver plays an important part in those well-recognized processes in which organic poisons of certain kinds are combined with intermediate products of metabolism, and by such combination are rendered inert.

That the combination of many aromatic poisons with sulphuric acid, which results in their excretion in the urine as aromatic sulphates, is carried out in the liver is indicated by the perfusion experiments of G. Embden and Glaessner.[80] As the outcome of their experiments, they concluded that the liver is the organ which plays by far the greatest part in the formation of ethereal sulphates,

but that small quantities of these compounds are also formed in the kidneys and in the lungs.

Another well-known protective process is the combination of aromatic compounds such as benzoic acid with glycocol, and their excretion in the form of hippuric acid and its allies. In this, it can hardly be doubted, the liver plays an important part, seeing that the observations of O. Zimmermann[81] indicate that the bile is the sole source of glycocol in the body. Zimmermann found that, in the case of a patient in whom all the bile was escaping through a surgical fistula, no hippuric acid was excreted in the urine after a dose of sidonal, whereas benzoic acid was abundantly present. When, at a later period, the fistula was closed the administration of benzoic acid produced a free excretion of hippuric acid.

These results have a wholly different significance from some earlier ones, in which conflicting results were obtained,[82] upon the excretion of hippuric acid by patients with hepatic disease, apart from the existence of biliary fistulæ. It may be noted that, even though the liver can alone supply the glycogen required, it does not necessarily follow that the actual synthesis occurs in that organ. That the kidney is the chief seat of the synthetic process there is good reason to believe, and that it is capable of effecting it has been conclusively shown by the experiments of Schmeideberg and Bunge.[83]

Some perfusion experiments by G. Embden[84] supply strong evidence that a third such protective process — viz., the combination of not a few poisonous substances with glycuronic acid —has its seat in the liver, although Embden thinks it probable that, as in the case of the ethereal sulphates, this synthesis is also carried out, to some extent, in other organs. In this connection the statement of van Leersum,[85] that the reducing power of icteric urines is attributable to glycuronic acid, is of interest.

That the various protective actions of the liver may be impaired in disease is *a priori* not improbable, but direct chemical evidence that this is the case is not yet forthcoming. Such evidence as is available rests upon the rather insecure basis of experiments on the toxicity of the urine, which indicate an increased toxicity in cases of grave hepatic disease.

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# CHAPTER XVI

# ANOMALIES OF METABOLISM

## Alkaptonuria and Cystinuria

By ARCHIBALD E. GARROD

These rare errors of metabolism have much more in common than is apparent at first sight, and it is probable that they are merely the most conspicuous members of a much larger group of metabolic anomalies which do not result from acquired disease, but are inborn, and the chemical analogies of structural malformations.[1] In both the derangement of the body chemistry is in itself practically innocuous, but cystinuria acquires a clinical as well as a scientific importance, owing to the great liability of the sparingly soluble cystin to be deposited in crystalline form and to produce urinary calculi.

Alkaptonuria and cystinuria are alike in their rarity, in their frequent occurrence in several members of the same family, and even in their essential nature, seeing that in both certain fractions of the complex molecules of proteins escape the destruction which they undergo in the normal human organism, and are excreted as such, or as intermediate products of their breaking down. A fresh link between them has recently been supplied by a case recorded by Ploos van Amstel,[2] in which the same patient exhibited both anomalies.

**Alkaptonuria.**—This name was originally bestowed on account of the rapid and conspicuous darkening which the urine of alkaptonurics undergoes when an alkali is added to it. The fresh urine is of normal colour, but it quickly acquires a smoky tint on exposure to air, becomes browner in time, and eventually as black as ink. Fabrics wetted with it become deeply stained, especially when they have dried slowly at the body temperature, and owing to this staining the condition is readily detected, even in infants. The darkening with alkalies, which is hastened by warmth, affords a colourable imitation of Moore's test for sugar, and a copious reduction occurs when the urine is heated with Fehling's solution.

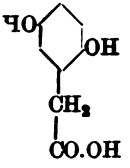
Ammoniacal solutions of silver nitrate are quickly reduced by it, even in the cold—a fact which is made use of in quantitative estimation. With Nylander's solution darkening occurs from the action of the alkali, but no reduction is obtained. No fermentation occurs with yeast, and the safranin reaction is not yielded. The urine is optically inactive. When a solution of ferric chloride is added, a few drops at a time, a deep blue colour appears, which lasts only for a moment, but it is necessary that the solution employed be very dilute, as otherwise the reaction is too rapid, and the blue colour is not seen.

The only morbid symptoms associated with alkaptonuria are some dysuria, which is occasionally complained of, and pigmentary changes in the cartilages, fibrous tissues, sclerotics and skin, the "ochronosis" of Virchow. That ochronosis is in some instances a result of alkaptonuria is no longer doubtful,[3] but a similar staining may be due to other causes, one of which is, beyond all reasonable doubt, the application over many years of carbolic acid dressings to chronic ulcers. In some of the alkaptonurics the ochronotic changes have been associated with lesions of joints, and a causal relationship appears not improbable.

There is no doubt that in most instances alkaptonuria is congenital, and persists throughout life. It has been detected in earliest infancy, and watched for many years. A few cases of temporary alkaptonuria are on record, but further study of such cases is much needed before it can be confidently stated that, in cases in which the urinary peculiarity is definitely proved to be temporary, the abnormal substance excreted is identical with that met with in congenital cases. The abnormality is wont to manifest itself in several brothers and sisters of a family, but very rarely in parent and child. A very large proportion of the affected families are offspring of marriages of cousins, and, as regards its heredity, the observed facts are most easily explained on the assumption that it is a recessive characteristic in the Mendelian sense.[4] Of the recorded cases, some fifty in all, the great majority have been in males, but, curiously enough, most of the temporary cases have been in females.

The essential feature of alkaptonuria is the excretion in the urine of an aromatic oxy-acid, and which is not met with, even in traces, in normal urine. It is to this substance, homogentisic acid, that all the peculiar properties of the urine are due, for homogentisic acid, a derivative of hydroquinone, has strong reducing powers, and yields a brownish-black oxidation product. It may easily be extracted as a crystalline lead salt or as an ethylic ester. The identity of the lead salt may be established by the determination of the water of crystallization and the percentage of lead contained in it; and from it the free acid, which melts at 146° to 147° C., may be obtained. The constitution of homogentisic acid is well

established, both by analyses and syntheses. It is 2 : 5 dioxybenzene acetic acid, and has the formula—



It has been found in the blood of alkaptonurics, but is not present in their fæces or sweat.

In addition to homogentisic acid, which was first isolated and investigated by Wolkow and Baumann,[5] a second substance, uroleucic acid, supposed to be hydroquinone $\alpha$-lactic acid, was formerly believed to have been present in the urine of some alkaptonurics. Recent investigations[6] have shown that this supposition was erroneous; that the evidence of the presence of a second acid is quite inadequate; that the substance to which Kirk[7] gave the name of "uroleucic acid" before homogentisic acid was known, and to which he assigned the formula $C_9H_{10}O_5$, was simply impure homogentisic acid; and that hydroquinone $\alpha$-lactic acid, which has been synthesized by Otto Neubauer, has quite a different melting-point from that assigned to uroleucic acid.

Only in containing homogentisic acid has alkapton urine been shown to differ from that of normal individuals. Ammonia is present in slightly increased amount, as the outcome of the ordinary mechanism for protection against acids. Uric acid, which was formerly believed to be diminished, has been shown to be present in the ordinary quantities.

Wolkow and Baumann showed that the output of homogentisic acid by alkaptonurics is conspicuously increased when tyrosin is given by the mouth. This indicates that the tyrosin fraction of proteins is one, at least, of its parent substances, and, indeed, protein foods increase the output in a like manner, and especially such proteins as are rich in the aromatic fractions. In normal individuals, on the other hand, the aromatic fractions of proteins, almost alone among aromatic compounds, are broken up, and the benzene ring therein is destroyed in the course of metabolism.

Falta and Langstein[8] found that phenylalanin must rank as a second parent substance of homogentisic acid, for it also increases the output as tyrosin does. On the other hand, tryptophane, which contains a benzene ring as part of the heterocyclic indol grouping, causes no such increase,[9] and its katabolism must be effected along a different line.

The increased output of homogentisic acid begins shortly after a protein meal, but the maximum is reached some four to six hours after the meal. The excretion of the alkapton acid precedes that

of the corresponding nitrogen. The tissue proteins, as well as those of food, contribute their quotum, as is clearly proved by the observations of Mittelbach, Langstein and Meyer, and Falta.[10] During periods of fasting, or of fat and carbohydrate diet, the excretion of homogentisic acid falls to some half of the normal amount, but never ceases.

Study of the $\frac{\text{homogentisic acid}}{\text{nitrogen}}$ or H : N ratio has revealed certain facts which are not brought out by that of the homogentisic excretion alone. Clearly, this ratio is determined by the proportion of tyrosin and phenylalanin in the proteins broken down, and will not be affected by changes in the quantity of protein katabolized so long as its quality remains constant. Thus, on a diet of uniform quality the ratio remains practically unaltered, even though the amount of food consumed vary. On the other hand, it undergoes conspicuous change when there is added to the diet a protein rich in aromatic fractions, such as casein, or one exceptionally poor therein, such as egg albumin.

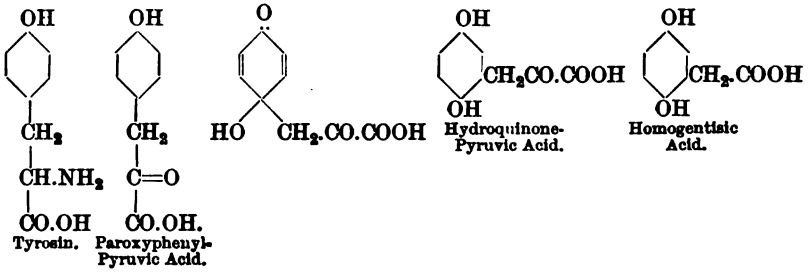
Falta arrived at the conclusion that, in the case which he studied, the metabolic error was complete, and that the homogentisic acid in the urine represented the whole of the tyrosin and phenylalanin of the proteins broken down. Although no comparative observations on different alkaptonurics on a diet of strictly uniform quality, such as milk alone, are yet available, determinations of the H : N ratio in several cases on mixed diet[11] strongly suggest that there is only one degree of alkaptonuria—namely, a maximal one—and that in all cases the breaking down of a given quantity of a given protein leads to the excretion of the same amount of homogentisic acid. On a mixed diet the H : N ratio is some 45-50 : 100. When milk forms a large constituent of the diet, as in some of the recorded instances, the ratios are considerably higher.

There is good reason to believe that homogentisic acid is an intermediate product of normal metabolism, which naturally undergoes destruction, and not an abnormal product which the alkaptonuric alone forms. A normal man must swallow a dose of 6 to 8 grammes of the acid in order that any of it may appear in his urine unchanged, whereas it is proved that an alkaptonuric has no such destructive power. It would be remarkable that, if the alkaptonuric alone has the power of forming homogentisic acid, he should also stand alone in completely lacking the power of dealing with it when formed. In some cases of hepatic disease and of diabetes the power of destroying homogentisic acid is much diminished, and it is argued by Grutterink and Hijmans van der Bergh[12] that in such cases large doses of tyrosin should produce alkaptonuria if homogentisic acid be a product of normal metabolism. However, such patients have not wholly lost their destructive power, and it may well be that, when tyrosin is administered to them, there is

at no moment a sufficient quantity of homogentisic acid in existence to overtax even their impaired power of disposing of it. Moreover, even in the case of alkaptonurics the yield of homogentisic acid only becomes quantitative when tyrosin is given in small and repeated doses. When a single large dose is given, the yield is comparatively small, and this suggests that in the normal man the power of forming as well as of destroying the alkapton acid is limited. By the administration of a number of aromatic compounds to alkaptonurics[13] it has been possible to gain some knowledge of the metabolic path from tyrosin and phenylalanin to homogentisic acid. No aromatic compound which, when swallowed by an alkaptonuric, does not increase the alkapton output can form a link in the chain, whereas a compound which does increase the output may do so. Space forbids any detailed discussion of the results of such experiments. Suffice it that it becomes evident that both the structure of the benzene ring and that of the side-chain exert important influences in connection with the processes in question. Halogen compounds of tyrosin are not converted to homogentisic acid, and Blum[14] has proved that neither ortho-tyrosin nor meta-tyrosin increase the alkapton output. Whereas phenyl *a*-lactic acid does cause an increase, phenyl *β*-lactic acid does not.

The shifting of the side-chain, which is involved, is probably effected through a stage of quinone linkage, as analogous shiftings suggest, and the investigations of Otto Neubauer[15] indicate that the first change is that of tyrosin to paroxyphenyl-pyruvic rather than to paroxyphenyl *a*-lactic acid.

Neubauer suggests the following as the most likely series of changes:




Experimental evidence can be adduced for each step in this series of changes, and for the exclusion of alternative steps. It should be mentioned that the assumption of a quinone grouping involves the further assumption that phenylalanin becomes converted into tyrosin as a preliminary step in its katabolism.

We may further suppose that down to this point the course of events is the same in the alkaptonuric and in the normal individual —in a word, that the above represents the normal katabolic path.

Where the alkaptonuric is peculiar is in that he does not destroy homogentisic acid, and disrupt its benzene ring. It would appear that in normal metabolism it is the presence of two hydroxyl groups in the 2 : 5 positions on the ring which determines its disruption, for, of the three dioxybenzoic acids, gentisic acid, which has its hydroxyls in that position, is alone to a great extent destroyed when it is administered to a normal man, whereas the alkaptonuric excretes it unchanged, just as he excretes its homologue, homogentisic acid.[16] Hence it would appear that the alkaptonuric is peculiar in that he does not possess the power which is possessed by a normal individual of breaking up aromatic compounds which contain two hydroxyl groups in the 2 : 5 positions on the ring. The anomaly is thus localized at a very late stage in the katabolism of the aromatic fractions of proteins.

The change in question is in all probability the work of a special enzyme, and is probably effected in the liver; for, as G. Embden and others have shown, perfusion of the liver with homogentisic acid or its parent substances leads to a formation of acetone, whereas aromatic compounds which are not destroyed in the normal organism have no such effect. We may suppose, then, that in the alkaptonuric the enzyme in question is lacking, or that its activity is in some way inhibited.

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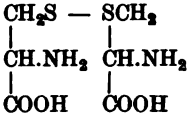
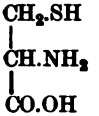
**Cystinuria.**—Cystin was discovered by Wollaston in a urinary calculus in 1810, and the sediments of hexagonal crystals were first described by Stromeyer in 1824 and Prout in 1825. It was not until some time later that it was recognized as containing sulphur. For many years the rare urinary calculi and sediments were the only known sources of cystin, and all attempts to synthesize the compound failed; but in 1899 K. A. H. Mörner obtained it by the hydrolysis of hair, and two years later G. Embden showed that it can be got in a similar way from egg albumin. Cystin now takes its place as a primary fraction of proteins, in which all, or nearly all, their sulphur is contained.

Friedmann proved that the formulæ which Baumann originally assigned to cystin and its derivative cystein were incorrect, and that the sulphur and the amino-group contained in it are attached to different carbon atoms, not to the same one, as was previously thought. The corrected formula are these:

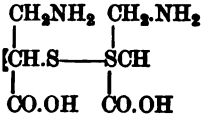


Cystin.



Cystein.

and they have been confirmed by the synthesis of this di-$\alpha$-amino-$\beta$-thio-lactic acid by Erlenmeyer junior. The isomer



has also been synthesized by Gabriel, and C. Neuberg and P. Mayer[1] have suggested that a second constituent of some cystin calculi, which crystallizes in needles, is this iso-cystin. However, doubt has been thrown on this, and Emil Fischer and Zuzuki[2] found that calculi which yield acicular crystals give Millon's reaction, and suggest that the needles are crystals of tyrosin. The great majority of calculi yield hexagonal crystals only, and do not give Millon's reaction.

In the normal organism the cystin fraction of proteins apparently undergoes more than one set of changes. The bulk of the sulphur of normal urine is fully oxidized, and in the form of sulphates. Another part, some 12 to 17 per cent. of the whole, is incompletely oxidized, and of this portion some can be more easily oxidized than the rest. Some of the cystin is doubtless utilized for the formation of the taurin of bile, and this is not wholly lost to the urine, but appears therein for the most part as neutral sulphur, and in part as taurin-carbamic acid.

Von Bergmann,[3] experimenting upon dogs with biliary fistulæ,

found that, whereas moderate doses of cystin, given alone, did not increase the biliary sulphur, a conspicuous increase resulted when cholalic acid was given with it. However, the possibility that cystinuria may be a secondary result of a defective supply of cholalic acid is negatived by the observations of C. E. Simon and Campbell[4] upon a cystinuric whose output of cystin was not affected by the administration of cholalic acid by the mouth. When a normal man takes cystin by the mouth, in doses of 5 grammes or so, it is wholly oxidized to sulphate, and appears as such in the urine;[5] but when larger quantities are given to animals, some is apparently decomposed in the alimentary canal, and its sulphur is excreted in the urine as thiosulphate. Baumann and Preusse[6] induced a kind of artificial cystinuria in dogs by the administration of chlor- or brom-benzene, which is followed by the appearance in the urine of mercapturic acids which are compounds of the halogen benzene with cystein. Mester[7] found that in human subjects only minute quantities of such compounds are produced. Friedmann has shown that the interpretation of these results is not affected by the revision of the formula of cystin, for the formulæ of the mercapturic acids needed revision in a like sense.

Cystinuria has been met with at all ages, and may undoubtedly persist for many years. Thus, Thompson crushed a cystin calculus in a man of eighty-one years, who had passed a similar stone thirty-nine years previously. The anomaly has repeatedly been exhibited by young children, and even by an infant of twenty-one months, but it has not yet been proved to be congenital. The cessation of deposits does not necessarily imply that the excretion of cystin has ceased, but it seems clear that in some instances the condition is temporary or intermittent. Cystinuria is rather less rare than alkaptonuria; the majority of its subjects are males. Brothers and sisters are wont to share the anomaly, and direct transmission from parent to child is observed in a considerable proportion of cases. It has been traced through several generations of a family.

The fæces do not contain cystin, but Dewar and Gamgee have detected it in the sweat.[8] In the case of an infant, a member of a cystinuric family, described by Abderhalden,[9] deposits of crystalline cystin were found in the viscera post mortem, and especially in the liver and spleen. This observation stands alone up to the present time.

The total output of sulphur in the urine of cystinurics is normal in amount, but the ratio of neutral to oxidized sulphur is conspicuously disturbed. The neutral sulphur is increased, and it seems certain that the unchanged cystin is excreted at the expense of the sulphates, and not of the normal neutral sulphur. Owing to the employment of different methods of estimation, and the unequal value of the methods used, our knowledge of the quantities of

cystin in the urine of different cystinurics is still very imperfect. In cases in which the more satisfactory methods have been employed, the daily output, on an ordinary mixed diet, has amounted to some 0·3 to 0·5 gramme.

It is evident that only a portion of the cystin of the proteins broken down is excreted unchanged, and it seems probable that some definite fraction of the total is concerned, but which that fraction is we do not know. The fact that in a case investigated by Wolf and Shaffer,[10] of a cystinuric with a biliary fistula, there was no evidence of diminution of the sulphur of the bile, suggests that the fraction in question is not that which normally goes to the making of taurin.

The evidence available indicates strongly that increase of protein food leads to an increased excretion of cystin in the urine of cystinurics. The observations of Alsberg and Folin,[11] and of Wolf and Shaffer, who carried out metabolic investigations over considerable periods, and who gave extreme dietaries, showed evident increase of neutral sulphur on a diet rich in protein as against one protein-free; and the recent work of Williams and Wolf,[12] who estimated the cystin itself by Gaskell's[13] method, show that the increase of neutral sulphur is actually in the form of cystin. Hele,[14] who also used Gaskell's method, was not able to give such extremes of diet, but his observations also show some increase of the cystin output when the protein of the diet was increased. However, it would appear that, just as under ordinary conditions only a part of the cystin of the katabolized protein is excreted unchanged, so, when protein is added to the diet, only part of the cystin of the added protein escapes destruction.

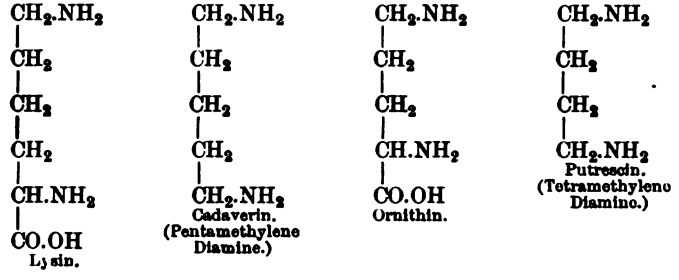
The results of the administration of cystin to cystinurics by the mouth are very interesting. Thus, when Loewy and Neuberg's patient swallowed cystin obtained by the hydrolysis of protein, he added the quantity taken to his ordinary output, whereas the patients of Alsberg and Folin, Thiele,[15] and Hele, burned it to sulphate. In Williams and Wolf's case some of the cystin taken was excreted unchanged. Loewy and Neuberg's patient was able to destroy cystin obtained from a calculus, in direct contrast to the result obtained with protein cystin in that case.

The metabolic error is not confined to the cystin fraction of proteins, for in some cases other protein fractions or their derivatives are met with in the urine. To Udranszky and Baumann[16] we owe the first demonstration of the presence of cadaverin and putrescin in the urine and fæces of a cystinuric. Since then cadaverin or putrescin, or both these diamines, have been met with in a number of cases, but in still more they have been absent—at any rate while the cases were under observation. Cadaverin has been found far more often than putrescin, and in the fæces they have seldom been detected. The same patient may excrete diamines at one period,

and not at another—at least in quantities which can be detected by the methods employed.

Udranszky and Baumann suggested that the diamines excreted might be formed by bacterial action in the intestine, but no positive evidence that this is the case is forthcoming, although cadaverin and putrescin are well known to be products of decomposition of proteins. It is much more probable that their presence in the excreta is a direct result of the metabolic error. This view gains powerful support from the fact that the patient of Loewy and Neuberg, who did not ordinarily excrete diamines in his urine, excreted cadaverin when he took lysin by the mouth, and putrescin when arginin was administered to him. In some other cases[17] in which arginin was so given no excretion of putrescin followed.

The formation of cadaverin from lysin, and of putrescin from the ornithin contained in arginin, is effected by the mere removal of $CO_2$ in each instance.




If the view that the diaminuria is due to the metabolic error be correct, we must suppose that they may be in part excreted by way of the intestine, and so appear in the fæces. Hele was unable to detect lysin itself in the urine of a patient who occasionally excreted cadaverin, but this diamino-acid has since been found by Ackermann and Kutscher[18] in the urine of a cystinuric.

Much more rarely tyrosin and leucin have been found in the urine of cystinurics, and their presence in one such case has been demonstrated beyond possibility of doubt by Abderhalden and Schittenhelm.[19] Loewy and Neuberg's patient did not excrete tyrosin, but when a dose of tyrosin was given by the mouth almost the whole of it was recovered from his urine, and a like result followed the administration of aspartic acid. The patient in question could deal well with proteins and with polypeptides, less well with dipeptides, such as glycyl-glycin, but failed to destroy the individual fractions disintegrated by the advanced pancreatic digestion of proteins. Other cystinuric patients to whom the individual amino-acids have been administered by C. E. Simon,[20] Alsberg and Folin, Thiele, Hele, and Garrod and Hurtley,[21] have not excreted them.

Alsberg and Folin and Wolf and Shaffer found an excess of

undetermined nitrogen in the urine of their patients, in whose urine no diamines nor amino-acids other than cystin could be found. The latter observers are inclined to attribute this to the presence of such substances in quantities too small to be detected by the ordinary methods.

It will be evident, from what has gone before, that cystinuria is due to a complex metabolic error of varying extent in different cases. The fact that the protein fractions involved are excreted as such, or in the case of the diamino-acids in the slightly altered form of diamines, suggests that the error lies at an early stage of protein metabolism, before deamidisation takes place. It is, moreover, obvious that we are here dealing with arrest rather than with perversion of the metabolic processes, but our knowledge is still too incomplete to allow of the framing of any theory which will satisfactorily explain the observed phenomena, and the differences of behaviour of the several cases investigated, especially towards individual protein fractions, including cystin, when administered as such.

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## CHAPTER XVII

# DIABETES MELLITUS, AND SOME OTHER CHANGES IN CARBOHYDRATE METABOLISM

By A. P. BEDDARD

Normal urine contains a small quantity of carbohydrate material. Besides dextrose, possibly maltose or isomaltose, and a dextrin-like body, there are always present compounds of glycuronic acid and a gluco-protein, mucin. The total copper-reducing power of urine varies between about 0·1 and 0·4 per cent., calculated as dextrose; after hydrolysis with a mineral acid the reducing power is increased by about one-third. It must not be forgotten that urates and creatinin are copper-reducing substances. Dextrose is the carbohydrate present in largest quantity, and its total daily excretion is probably not more than 1 gramme. The quantity of carbohydrate in urine may be altered by the excretion either of the usual constituents in abnormal quantities, or of carbohydrates, such as lævulose, galactose, lactose, pentose, etc., which are excreted only when exceptional peculiarities of diet or metabolism are present.

### A. Diabetes Mellitus.

An increase of dextrose in the urine does not necessarily indicate that diabetes is present. A healthy man cannot eat unlimited quantities of all carbohydrates without producing glycosuria. The amount of starch is limited only by power of digestion; but in the case of the sugars there is a definite quantity which will cause glycosuria when eaten in a single dose, and especially on an empty stomach. The quantity varies both with the individual and with the kind of sugar eaten. This difference between starch and the sugars is due only to the greater rate at which sugars are absorbed; and it is found that even dogs with an Eck's fistula do not show glycosuria after eating starch. On an average glycosuria is produced in a healthy man by more than about 200 grammes of dextrose or saccharose and 50 to 100 grammes of maltose, and lævulosuria by about 200 grammes of lævulose, and lactosuria by 50 to 100 grammes of lactose. These physiological alimentary

glycosurias are not diabetes. When, however, the eating of starch or of an unusually small quantity of one of the sugars, which yield dextrose, causes glycosuria, the condition must be considered pathological, and we say that the patient is suffering from diabetes; in fact, pathological alimentary glycosuria is a constant feature of diabetes, and can always be induced by an appropriate diet.

Carbohydrates undergo changes both in the alimentary canal and the tissues. In physiological and pathological alimentary glycosuria the failure to cope with the excessive quantity of carbohydrate takes place generally in the tissues rather than in the alimentary canal; consequently the larger part of the sugar excreted is not that of the food, but in the form into which the food has been transformed in the alimentary canal. Starch is converted in the intestines wholly into dextrose, and this sugar alone will be excreted in the urine. Lactose is split by the intestinal lactase into dextrose and galactose. If any lactose is absorbed as such, lactosuria is produced. Galactose is converted by the liver into dextrose, and any galactose which escapes through the liver will be excreted unchanged. After large doses of lactose, both galactose and dextrose may be found in the urine. Maltose is converted in the intestine into dextrose. A physiological maltosuria has not been observed; the only sugar known to be excreted after an administration of maltose is dextrose. Cane-sugar is split by the intestinal invertase into dextrose and lævulose, and any cane-sugar which escapes the action of this ferment is excreted unchanged. Lævulose is transformed by the liver into dextrose; any which escapes this conversion is excreted unchanged, and after excessive doses of cane-sugar both lævulose and dextrose may be found in the urine.

The abnormal condition of the urine in diabetes is the direct result of an altered composition of the blood, which in turn is caused by changes in metabolism. Human diabetes, however, is not a single disease, but a collection of pathological conditions which have only one symptom in common—namely, a reduction in the power of the tissues to assimilate carbohydrate which has undergone its normal transformation in the alimentary canal. We have to consider the nature of these pathological conditions, what in metabolism they produce, and how they do so; but before doing so it is necessary to have a working conception of normal carbohydrate metabolism in so far as it concerns the formation and utilization of dextrose in the body.

**Normal Carbohydrate Metabolism.**—The carbohydrate in the food is digested chiefly into dextrose, which is absorbed as such into the portal blood. The dextrose on reaching the liver is converted into, and temporarily stored as, glycogen. This store is drawn upon by the tissues; the glycogen is reconverted into dextrose, which passes to the tissues and may be temporarily stored there a

second time as glycogen. The conversion of glycogen into dextrose in the liver and muscles is brought about by ferment action, and the opposite change is possibly due to a reversed action of the same ferment. Galactose and lævulose lead to a deposit in the liver of the same glycogen as that produced from dextrose, and this must mean that the cells of the liver have the power of making them undergo an isomeric transformation into dextrose. The result of the deposition of glycogen in the liver and muscles is that large quantities of carbohydrate food can be eaten without producing at once hyperglycæmia and alimentary glycosuria.

The quantity of sugar in systemic blood appears to be fairly constant in health, and is probably something less than 0·2 per cent. About half of this amount is present as free sugar, about a quarter in loose chemical combination with protein or lecithin, and the remainder as a hydrolysable sugar or polysaccharide. The sugar is present only in the plasma, and more than half of it is dextrose.

The storage of glycogen in the liver and muscles is very limited in extent. A liver of 1,500 grammes might contain 10 to 20 per cent. of glycogen, and therefore store about 300 grammes of dextrose, and the muscles, by holding 1 per cent. of glycogen, might account for an equal quantity of dextrose; but most men eat at least 250 grammes of carbohydrate a day, and many double that amount. The question arises as to what happens to carbohydrate food which is not stored as glycogen. The 3 litres of blood in an adult's body would not contain more than 3 to 6 grammes of free dextrose at any moment, and the tissues generally, when perfectly fresh, do not hold more than traces. The rise in the respiratory quotient after eating carbohydrate shows that an increased quantity of dextrose is used by the tissues, but in the absence of muscular exertion the amount immediately disposed of in this way is probably not very great. The ultimate conversion and storage of carbohydrate as fat is certain; the only doubt is whether this transformation is necessarily a very slow process. Dextrose, chiefly in the form of glucosamine, is found in combination in a large number of proteins. Gluco-proteins, such as mucin, may contain 30 per cent. of glucosamine, but the more abundant proteins, like serum globulin and serum albumin, possess at most 1 to 2 per cent. We may therefore conclude that the quantity of free dextrose in the body is very small, that glycogen may be present to the extent of 0·5 to 1 kilogramme, and that dextrose, in the form of glucosamine, amounts to 0·5 kilogramme, and possibly a good deal less. In other words, the store of carbohydrate in the body is never large, and in many people considerable quantities of carbohydrate must be converted into fat and stored as such.

The smallness of the carbohydrate store necessitates the belief that glycogen and dextrose may be derived from protein or fat.

The proof of this has been obtained largely by a study of diabetes. For instance, a diabetic patient, on a diet free from carbohydrate, may excrete 1 kilogramme of dextrose a day. Again, Pflüger found that a depancreatized dog fed upon protein free from glucosamine excreted in two months 2·5 kilogrammes of dextrose more than could possibly have been obtained from the carbohydrate stored in its body. Although strict proof is wanting that proteins can be converted directly into glycogen and dextrose, the evidence in favour of this view is very strong, and we may safely assume its truth. The method of this conversion can only be guessed at. Proteins are hydrolysed by the digestive ferments into amino-acids which undergo deamidisation during absorption ; simple fatty acids therefore are liberated, and from these, such as simple derivatives of lactic acid, dextrose must be synthesized. As a proof of this it had been shown that glycin, leucin, alanin, etc., when given in the food in diabetes, lead to an increased excretion of dextrose. In diabetic patients the ratio of the dextrose to the nitrogen excreted in the urine may be so high on a diet free from carbohydrate that it is impossible for all the dextrose to have been derived from protein, and consequently some of it must have come from fat. In the process of the oxidation of fat in the body it is probable that the long chain of the higher fatty acids is demolished by the removal of two carbon atoms at a time until a lower fatty acid is produced. Carbohydrate must be formed from fat, just as it is from protein, by a synthesis starting from derivatives of simple fatty acids. Again, glycerine must be liberated from neutral fats both in the alimentary canal and the tissues, and we know that glyceric aldehyde, which is isomeric with lactic acid, polymerizes into sugars. Further, there is experimental evidence which suggests that glycerine added to the food may be converted into glycogen and dextrose in the body. We see, therefore, that the synthesis of sugar from protein and fat has been established as one of the chemical reactions of diabetic metabolism, which, however, is a pathological condition. Nevertheless, the reaction probably occurs in normal metabolism, and would be made use of when the tissues were not being supplied with sufficient dextrose derived from carbohydrate food. There is no reason to think that sugar obtained from fat or protein must be converted into hepatic glycogen before it passes to the tissues as dextrose.

We must now consider the utilization of dextrose as a source of energy. We know that it is oxidized in the tissues, and leaves the body as $CO_2$ and water ; but it is important to remember that the oxidation of dextrose takes place in steps with the production of numerous intermediate products, and that sugars can be converted into very much simpler compounds without liberating any energy. For instance, it is probable that the lactic acid found in so many tissues is derived, in part at least, from glycogen or dextrose ;

possibly glyceric aldehyde is an intermediate step. Further, lactic acid may be a stage in the alcoholic, butyric, and acetic fermentations of sugar ; but during the conversion of sugar into lactic acid, and even into acetic aldehyde or formic acid, there is no evolution of energy. In other words, we have to look upon the utilization of dextrose as taking place in a series of changes preliminary to the liberation of energy by the final oxidation of extremely simple compounds. The number of intermediate substances into which dextrose is transformed is probably very great, and of these lactic acid is a late one (in the process of oxidation). It is probable that dextrose undergoes a stereo-isomeric transformation into galactose, for carnivorous animals can continue to secrete lactose on a diet of pure meat. It has been shown that glycuronic acid in rabbits is derived from dextrose by the oxidation of the terminal secondary alcohol group. It has been found that certain bacteria can split off $CO_2$ from glycuronic acid and produce *l*-xylose ; therefore there can be little doubt that this pentose, which is necessary for the synthesis of nucleic acid, comes from dextrose. Lastly, glycerine can certainly be formed in the body ; it can be converted into sugar by the tissues, and if glyceric aldehyde is a stage in the production of lactic acid from dextrose, there are grounds for looking upon dextrose as a source of glycerine.

The above considerations indicate that, in metabolism, proteins, fats, and carbohydrates, are to some extent interchangeable, and that lactic acid or some simple derivative of it constitutes one common stage in their katabolism. These simple compounds may be dealt with further in two ways: either they may be oxidized directly and made to yield energy, or they may be built up into fats, carbohydrates, or the non-nitrogenous part of protein. The factor that determines which of these two processes shall take place, and, when synthesis occurs, whether fat, carbohydrate, or protein, shall be formed, must be the needs of the tissues ; but we are profoundly ignorant how the tissues make their needs felt and bring about the desired result.

When we turn to the question of where and by what means the molecules of dextrose are disintegrated, we can make very few positive statements. Lépine has paid much attention to the glycolytic action of fresh blood, which was described originally by Claude Bernard ; but even granting that blood has a feeble glycolytic action, it is none the less true that the metabolism of the body as a whole is carried on within cells, and not in the blood or any extracellular fluid. The utilization of a foodstuff by a cell includes a number of processes of which we understand next to nothing. We believe that a foodstuff becomes attached to something in protoplasm, and is then acted upon by one or a series of intracellular ferments which form a combination with it, and are specific because they possess the stereo-chemical configuration

necessary for combination with the foodstuff in question. We should imagine, therefore, that ferments in such cells as those of muscle would be an important factor in glycolysis, and we know, from a study of experimental pancreatic diabetes, that the pancreas produces a hormone which is essential to the utilization of dextrose by cells. Cohnheim has published experiments which appear to demonstrate the factors concerned in glycolysis. He found that the juice expressed from fresh muscle possessed next to no glycolytic action unless a boiled or alcoholic extract of pancreas were added. He therefore put forward the view that the pancreatic hormone activates a glycolytic ferment present in muscle. The products of this glycolysis were not determined further than that acids were formed. Other observers have failed to obtain these results, or, having obtained them, have ascribed them to bacterial action. But Cohnheim's results have been confirmed, and on the whole the balance of evidence is in favour of his view. As we should expect, the reaction is specific for dextrose, and other sugars, such as lævulose and galactose, are unaffected by it. Further, although the degree of glycolysis observed *in vitro* is not great, it cannot be supposed that expressed muscle juice and the mode of experiment reproduce even approximately the conditions which exist in the interior of living cells. It seems probable that the pancreatic hormone acts as an amboceptor which attaches dextrose to something in protoplasm, and allows intracellular ferments to act upon this sugar and convert it either into glycogen or into simpler bodies, from which energy is ultimately obtained.

A consideration of normal carbohydrate metabolism shows that the free carbohydrate of the body is derived generally from that in the food, and only where required, from protein or fat; further, it shows that carbohydrate food does not lead to hyperglycæmia because the tissue can utilize dextrose rapidly, and can store it as glycogen, fat, or in combination with protein.

When we turn to human diabetes, we find that the glycosuria is always due to hyperglycæmia. There is no certain evidence that a variety of diabetes occurs comparable to phloridzin diabetes and certain other experimental forms, in which glycosuria is due, not to hyperglycæmia, but to the kidney cells being stimulated either to excrete dextrose free in the blood or to split off combined dextrose. In man such a renal form of diabetes has been described, but probably on insufficient evidence. At most there may be men, just as there are animals, whose kidneys, under the influence of diuretic substances, excrete dextrose with an unusual ease.

Hyperglycæmia might be caused theoretically in a variety of ways, but of these only the following are known to contribute to this condition in diabetes: 1. Impairment of the glycogenic function of the liver and muscles, caused by the cells being unable to store dextrose as glycogen. This defect would be apparent only after

carbohydrate food, and would be more marked after sugars than after starch. We should expect that a large carbohydrate meal would cause a sudden and severe hyperglycæmia, that the excess of sugar in the general circulation would be excreted by the kidneys before much of it could be stored as fat, and that the resulting glycosuria would not be continuous, but bear a definite relation in time to the meals, and be, in fact, a typical alimentary glycosuria. 2. Impairment of the power of the muscles and other tissues to utilize dextrose. 3. Overproduction of dextrose from glycogen, protein, or fat. With these two defects we should expect a more continuous hyperglycæmia and a glycosuria showing a less definite relation to meals; and in order to explain the presence of hyperglycæmia it would be necessary, further, to imagine that the dextrose which either was not utilized or was overproduced could not be converted wholly into fat and used in that form.

The pathology of many cases of diabetes is so uncertain or obscure that it is difficult, if not premature, to attempt a classification based upon the pathological conditions underlying the metabolic changes; but from the point of view of metabolism diabetic patients may be divided roughly, and as a matter of convenience, into two great groups: (1) Cases of *mild diabetes*. In them the glycosuria ceases as soon as the carbohydrates in their food have been sufficiently reduced. In most of these cases the glycosuria depends entirely upon the quantity or kind of carbohydrate in the food; but in a few cases the glycosuria is increased when very large quantities of protein are eaten. (2) Cases of *severe diabetes*. In them the glycosuria does not cease as soon as their diet is freed from carbohydrates. They must therefore excrete dextrose derived from protein or fat as well as from carbohydrates. In the least advanced of these cases the glycosuria stops in the course of prolonged treatment by a diet free from carbohydrates; in more advanced cases the glycosuria never stops unless the quantity of protein is restricted as well as carbohydrates eliminated from the food, and in the most severe cases the glycosuria persists in spite of treatment. These two great groups of cases, from a pathological point of view, may correspond both to different stages in the same pathological condition and to altogether distinct pathological conditions. For all cases of severe diabetes have probably been through a stage corresponding to that of cases of mild diabetes, but some cases of the mild type of the disease never show any tendency to progress into cases of the severe type.

I. **Mild Diabetes.**—Diabetes with a metabolism characteristic of this type may be divided into four varieties, in accordance with the pathological condition which causes the change in metabolism.

1. **Neurogenous Diabetes.**—The knowledge that there is a form of diabetes caused by the action of the nervous system upon the

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1. **Neurogenous Diabetes.**—The knowledge that there is a form of diabetes caused by the action of the nervous system upon the

liver is based upon Claude Bernard's experiments with diabetic puncture. He showed that puncture at the tip of the calamus scriptorius in the fourth ventricle is followed generally by hyperglycæmia and glycosuria, but sometimes only by polyuria. The glycosuria begins at once, and disappears in the rabbit within a day, and in the dog within a week. At the end of the experiment the hepatic glycogen is found to have disappeared, that in the muscles probably is unaffected, and no other change in metabolism is observed. These facts suggest that the hyperglycæmia, in part at any rate, is due to a too rapid conversion of glycogen into dextrose. An explanation of these results was sought in the supposition that the puncture of the medulla produced stimulation, and not destruction, of a hypothetical diabetic centre. The probability of this view was supposed to be shown by the fact that stimulation of afferent nerve fibres, such as those in the vagus, the sciatic, or depressor, also produced glycosuria. The path of the efferent impulses in this reflex was thought to be by the spinal cord, the upper thoracic spinal roots, the sympathetic chain, and thence by the splanchnic nerves to the liver. Stimulation of any part of this reflex arc caused the hepatic glycogen to be converted rapidly into dextrose, and therefore produced hyperglycæmia.

Recent work, however, has thrown doubt on this simple explanation. In the first place, it is very doubtful whether stimulation of afferent nerves causes glycosuria by a direct effect upon the diabetic centre. It has been found that stimulation of the central end of the vagus does not produce hyperglycæmia when the animal is freely supplied with oxygen, and the interference with respiration no longer produces partial asphyxia. It is known that any interference with respiration, such as obstruction of the air-passages, severe anæmia, poisoning with strychnine, curare, HCN, CO, etc., if sufficiently severe to produce marked dyspnœa, will cause glycosuria; and there are experiments which seem to show that either a deficiency of oxygen or an increase of $CO_2$ in the blood may cause this result. Asphyxia causes a disappearance of hepatic glycogen, but is not known to do so by stimulation of the diabetic centre, although this is possible in some cases.

A study of various drugs which produce dyspnœa and glycosuria indicates that the relation between asphyxia and glycosuria is complex and imperfectly understood. Thus, it has been shown that the intravenous injection of a strong solution of NaCl causes dyspnœa, increases the permeability of the kidney to dextrose, and probably accelerates the conversion of hepatic glycogen into dextrose. Again, it has been found that all anæsthetic substances, such as chloroform, ether, nitrous oxide, morphia, $CO_2$, etc., produce hyperglycæmia. Anæsthetics combine with tissue proteins, and it is possible that by combining with the proteins of protoplasm they turn out and liberate carbohydrate. It is further possible in

the same way that they may liberate the dextrose in loose chemical combination in the blood-plasma.

In the second place, recent work has shown that efferent glycogenolytic fibres cannot be demonstrated in the cut spinal cord or in the great splanchnic nerves after section, probably because of the great fall in arterial blood-pressure which is caused. Stimulation of the uncut splanchnics, however, does cause hyperglycæmia. The nature of the impulses carried to the liver by the splanchnics is uncertain; they might be vasomotor, but it seems more likely that they influence directly the cell protoplasm so that the conditions necessary for the production and action of the diastatic ferment upon glycogen are favoured. It is impossible to say whether these impulses influence the power of the cells to manufacture glycogen from dextrose. Adrenalin injected intravenously has the same action as electrical stimulation of sympathetic nerves, and it is probable that adrenalin glycosuria is similar to that produced by stimulation of the great splanchnic nerves. In both cases the circulation through the pancreas would be interfered with, and possibly these glycosurias, if prolonged, might become partly pancreatic in origin.

We believe at present that the hyperglycæmia following diabetic puncture is due to dextrose produced from hepatic glycogen, and that this conversion is an overproduction because it takes place irrespectively of the needs of the tissues. In fact, this is the only kind of diabetes in which the primary defect in carbohydrate metabolism is an overproduction of dextrose.

In man there are some cases of diabetes which certainly, and others which probably, are due to the same changes as are produced by diabetic puncture and the stimulation of the various afferent and efferent nerves in Claude Bernard's experiments. In rare cases painful affections of the peripheral nerves, such as the trigeminal and sciatic, and tumours pressing upon the vagus, have been accompanied by glycosuria. Tumours of the medulla, pons, and cerebellum, atheromatous and syphilitic disease of the cerebral arteries, cerebral hæmorrhages, fractures of the base of the skull, etc., may cause glycosuria, presumably by direct stimulation of the diabetic centre. In all these conditions, just as after diabetic puncture, there may be a polyuria which is independent of the presence or absence of glycosuria. A number of conditions may be mentioned in which possibly the diabetic centre is stimulated from higher parts of the brain; such are general paralysis, mania, delirium tremens, meningitis, neurasthenia, traumatic neuroses, exophthalmic goitre, etc. Carbohydrate metabolism certainly can be influenced by the higher parts of the brain, because all forms of diabetes may be aggravated by psychical disturbances.*

A review of the various conditions which cause neurogenous

See p. 621, where another explanation of neurogenous diabetes is given.

such. In normal men it is found that alimentary glycosuria can be produced much more readily when they have been receiving large quantities of carbohydrates and their tissues are already filled to their utmost capacity with glycogen. It is impossible to say whether the glycogenic function of the tissues could be permanently impaired by overworking the cells for a long period.

These considerations make it very doubtful whether lipogenous diabetes is a distinct pathological variety. It seems probable that any case of mild diabetes, due to arterio-sclerosis, hepatic or pancreatic disease, etc., whose appetite and digestion are good and whose food more than covers the bodily requirements and the loss of energy, as dextrose, in the urine, may be fat like a healthy person would be under the same circumstances. There can be no doubt about the clinical fact that many diabetic patients become suddenly and rapidly obese in the earliest stage of their disease; and we may suppose that they store and utilize as fat carbohydrates which in healthy people would have been stored and used as carbohydrate.

4. **Pancreatic Diabetes.**—Pathologists had long known that diabetes might be associated with disease of the pancreas, but it was not until physiologists had produced diabetes by partial or complete removal of the pancreas that the connection was understood. Sandmeyer showed in dogs that when less than about four-fifths of the pancreas were removed neither glycosuria nor any other change in metabolism took place. When, however, only about one-fifth of the gland was left, a mild form of diabetes was produced. At first glycosuria was present only when carbohydrate food was eaten, and even when a dog ate 500 grammes of bread and 1 litre of milk a day the quantity of dextrose in the urine was often less than 1 gramme. During starvation or when a diet of meat was given the glycosuria disappeared. Very large quantities of meat might produce glycosuria. The dogs did not lose weight. The digestion and absorption of proteins and fat were less good than in the intact animal, presumably owing to the absence of pancreatic juice; but absorption is much better after partial than after complete removal. This fact shows that there is another factor concerned, and suggests that an internal secretion of the pancreas is concerned in the absorption of fat and protein. At first the metabolism of these animals was normal in all other respects, and their livers and muscles contained large quantities of glycogen. In the course of several months the remnants of pancreas underwent a slow atrophy, other changes of metabolism appeared, and the animal passed into a condition identical with the severe diabetes produced by complete removal of the pancreas, which we shall have to consider in detail later; suffice it to say here that a partial failure of the internal secretion of the pancreas induces a mild form of diabetes which appears to correspond

to a similar failure of the glycogenic function of the liver and muscles.

The form of mild diabetes under consideration is pathologically distinct, but clinically there is nothing in the glycosuria to distinguish it from the other varieties already considered. The glycosuria in its slightest form is only alimentary either *e saccharo* or *ex amylo;* later it becomes continuous, but depends upon the presence of carbohydrate in the food. We know, however, that if the lesion progresses sufficiently the diabetes changes from the mild to the severe type, and of no other variety of mild diabetes is this known to be true.

In man the pancreas may be destroyed by growth; it may undergo fibrosis as a result of cirrhosis of the liver, of infection ascending its duct, and of obstruction of its duct by calculi or growth. Arterio-sclerosis of the pancreatic arteries may produce a granular atrophy of the acini, a replacement fibrosis and lipomatosis of the gland, and hyaline changes in its capillaries. The whole gland may be destroyed by acute hæmorrhagic pancreatitis, and the patient die before diabetes has had time to develop. It is impossible to say how far the transient glycosurias seen in alcoholic, febrile, and other intoxications are of pancreatic origin; nor do we know whether adrenalin, pituitary extract, etc., can influence the functions of the pancreas by interfering with its blood-supply. Possibly the gland may have its functions upset by nervous and psychical influences, as is undoubtedly the case with the stomach.

When we have to decide the pathology of a given case of mild diabetes, it is not difficult to account for the glycosuria if a lesion of the pancreas or brain is present; and the same is true of lesions of the liver, although in this case it may be difficult to say how far it is the liver, and not the pancreas, which is at fault. But when no such lesion can be found the difficulties are very great, and we are obliged to fall back upon nervous, toxic, and functional disturbances of these organs. There are other tissues disease of which theoretically might produce diabetes. For instance, a widespread disease of muscle might cause diabetes in accordance with Cohnheim's view, just as does disease of the pancreas; no such condition, however, is known. Again, disease of the intestine might have the same effect as disease of the pancreas; for we are bound to believe that carbohydrate food must liberate a hormone which will stir up the pancreas to produce its internal secretion. Possibly the glycosuria observed in cholera is of this nature; if so, it is the only known instance of a primary intestinal diabetes.

II. **Severe Diabetes.**—The essential feature in the metabolism of these cases is that they excrete dextrose derived, not only from carbohydrate food, but also either from tissue fat or from protein food, or from both sources at the same time. Little was understood about their pathology and metabolic changes until v. Mering and

Minkowski showed that a similar condition was induced in mammals by complete removal of the pancreas. They further proved that the altered metabolism was due to the absence of an internal secretion. This becomes clear from the following observations: Tying the pancreatic duct does not cause glycosuria. The diabetes may be prevented by grafting a sufficient portion of the animal's own pancreas previous to the removal of the remainder, and when the graft is cut out glycosuria sets in at once. The absence of the pancreatic juice reduces by at least 50 per cent. the absorption of fats and proteins. Feeding the animals with raw pancreas improves the absorption considerably, but it neither raises it to the normal nor prevents the glycosuria. There is no doubt that complete removal of the pancreas always produces severe diabetes in mammals, and that the failure to produce diabetes, which has been noted occasionally, is due either to anatomical difficulties in certain animals or to the presence of accessory pancreatic tissue in the wall of the duodenum and elsewhere.

After complete removal of the pancreas the animal suffers from hunger, thirst, and polyuria; it wastes rapidly, and dies within three weeks. The cause of this rapid death is not the severity of the diabetes, but infection of the wound and suppuration. In men suffering from diabetes it is difficult to prevent wounds from suppurating, and in animals it is practically impossible. The difficulty has been got over either by performing Sandmeyer's operation or by grafting. The wound then heals, and it is only after the remnants of pancreas or the graft have slowly atrophied that hyperglycæmia begins. Animals operated upon in this way live for weeks after the onset of severe diabetes.

When the gland has been removed, glycosuria sets in within a few hours, and lasts until death. It continues when the animal is having food which is free from carbohydrate, and also during complete starvation. Post mortem the liver and muscles contain either no glycogen or but very little, and the subcutaneous and other deposits of fat have disappeared, but the liver is extremely fatty. When known quantities of carbohydrate food are given, the diabetes is found to be complete—that is to say, the absorbed carbohydrate is excreted nearly quantitatively in the urine. In the case of starch, maltose, and dextrose, the urine contains only dextrose. Galactose in the food is excreted chiefly as dextrose, only small quantities of galactose appearing in the urine; and lactose, which yields on hydrolysis dextrose and galactose, reappears in the main as dextrose. Lævulose is an important exception. If large quantities of this sugar are given, the excretion of dextrose is increased, and some of the lævulose is found in the urine; but if the quantity given is only small, no lævulose is excreted, and the increase of dextrose in the urine is only slight. This shows that lævulose can be utilized, and the same is true to a less extent of galactose. We

know, further, that lævulose causes glycogen to be found post mortem in the liver and muscles, and also raises the respiratory quotient, and that these are true neither of dextrose nor of carbohydrates which yield dextrose. Inulin, a polysaccharide which is hydrolysed wholly into lævulose, has the same effect as lævulose; and cane-sugar, which yields dextrose and lævulose, causes an increased excretion of dextrose which corresponds to not much more than half of the sugar administered. The excretion of dextrose is not increased by fat in the food, but it is by protein, even when the protein contains no carbohydrate radicle. The nitrogen and dextrose in the urine are found to bear a fairly constant ratio to each other, which is never higher than about 3, and this ratio is not altered by giving protein food. The urine contains acetone, diacetic and $\beta$-oxybutyric acids.

When we turn to pancreatic diabetes in man, we find that it reproduces in a less acute form the metabolic changes observed in experimental pancreatic diabetes. We may therefore conclude that they represent the same condition, and that we may safely argue from one to the other. We have now to consider in detail what these metabolic changes are, and how they are produced by failure of the internal secretion of the pancreas. It will be convenient to discuss the subject under the following heads:

1. **The Glycogenic Function of the Liver and Muscles.**—In animals the glycogen is either reduced in quantity or absent, in accordance with the completeness with which the pancreas has been removed. In man it is probably true that, the more severe the pancreatic disease, the greater is the reduction in the quantity of glycogen. This reduction might be due to the cells either being unable to form glycogen, or to their being able to make it but not to retain it, or to both causes combined. We know that the liver can manufacture glycogen from lævulose and retain it, and that it cannot do so from dextrose. And since we believe that the cells have to convert lævulose into dextrose before they can deposit it as glycogen, we must conclude that the liver cells would also be able to convert the dextrose of the food into glycogen, if only they could get hold of it. In other words, these data suggest that in pancreatic diabetes the cells of the liver have lost the power of picking up dextrose from the portal blood, and that they still retain the affinity necessary to fix lævulose, and to a less extent galactose. If this is so, then the hormone provided by the pancreas must be concerned in the fixation of dextrose by the cells of the liver and muscles. Since the glycogen formed from dextrose and from lævulose is the same, and since the hepatic cells can retain some of that formed from lævulose, there is no reason to think that there is any loss of the power of these cells to retain the glycogen which they have formed. We therefore conclude that in pancreatic diabetes the cells of the liver and muscles, owing to a diminution or absence of the internal

secretion of the pancreas, have lost, partially or wholly, the power of picking up dextrose brought to them in the blood; consequently, when carbohydrates which yield dextrose are eaten, hyperglycæmia and a pathological alimentary glycosuria are produced.

Pflüger has formed a different conception of the trouble. He believes that the power of the hepatic cells to form glycogen is unimpaired, and even very active, but that they cannot retain glycogen, because of the absence of the pancreatic hormone, which is an antidiastase and controls the activity of the diastatic ferment in the liver. There are, however, the following objections to Pflüger's view: The activity of the diastatic ferment in livers taken from depancreatized dogs is not found to be greater than normal, nor does a boiled extract of pancreas have any inhibitory effect *in vitro* upon the activity of this ferment. Further, an antidiastase would not explain why the same glycogen formed from dextrose and lævulose should be retained in the liver in the one case, and not in the other.

It must not be thought that in diabetes the liver necessarily retains its full power of converting lævulose and galactose into dextrose. In cases of mild diabetes 200 grammes of lævulose may be given without producing glycosuria; but in a severe case 50 grammes of lævulose administered daily may lead at first to an increased excretion of dextrose, and then to lævulose appearing in the urine in increasing quantities. Further, there are many cases of severe diabetes in which lævulose is utilized no better than dextrose. The explanation of this seems obvious. Lævulose by being converted into glycogen will not produce the alimentary glycosuria which would be caused by a carbohydrate yielding dextrose. But this glycogen will leave the liver as dextrose, and when the muscles and other tissues have lost the power of utilizing dextrose, lævulose will be no better as a food than dextrose. There are, however, amongst diabetic patients great individual differences in their powers of assimilating various monosaccharides and disaccharides. Thus, lactose may be utilized better than lævulose or dextrose by some patients, and less well by others. More difficult to understand are individual differences in the power of assimilating starches from various sources, such as bread, potatoes, and oatmeal. The explanation cannot be found either in the absorption of different quantities from the intestines or in the blood-obtaining diastatic ferments which are specific for the particular kind of starch which is being given. The rate at which different starches can be digested, and therefore absorbed, might explain the phenomenon.

It must be remembered that ordinary dextrose—*d*-glucose—represents the point of equilibrium of a mixture of two isomerides, *a*-glucose and *β*-glucose, which have different specific rotatory powers and a different stereo-chemical configuration of their mole-

cules. It has been suggested that, when a ferment acts upon a substance—the substrate—it forms a compound with it, and that the specificity of ferments is due to their being unable to combine with the substrate unless they have the corresponding stereochemical configuration. The same is possibly true of the combination of dextrose with protoplasm. The relative proportion of $\alpha$- and $\beta$-glucose present in a solution varies with circumstances. We do not know what this relation is in health, and whether it is disturbed in diabetes. But it is possible that research along this line might give the clue to many phenomena in diabetes which are at present impossible to explain.

2. **The Utilization of Dextrose by the Tissues.**—There are many observations which show that in pancreatic diabetes there is a partial or nearly complete inability of the muscles and other tissues to utilize and obtain energy from dextrose. We have already mentioned some of them, such as the fact that, when carbohydrate is added to the food, it may be excreted nearly quantitatively in the urine; the fact that the glycosuria persists during complete starvation, and when only pure protein is being eaten. And since there is no reason for thinking that dextrose derived from protein or fat is metabolized by cells in a different way to that derived from carbohydrate, we conclude that the cells in severe diabetes have lost more or less the power of utilizing dextrose, from whatever source it may be derived. There are other observations which point to the same conclusion. We have seen that in cases of mild diabetes muscular exercise and fevers increase the quantity of dextrose utilized by the tissues, and therefore reduce the glycosuria; but in severe diabetes exercise and fever often have no such effect, and may even increase the excretion of sugar. Again, the respiratory quotient may be very low—less than 0·7—less, in fact, than the value observed in normal men during complete starvation. This very low value has two causes. In the first place, carbohydrate is being obtained from fat, and is not oxidized further, just as is the case in hibernating animals; and, in the second place, the body is no longer utilizing carbohydrate, no matter what its source may be. Consequently, in the most severe cases of diabetes it is found that carbohydrate food does not lead to any rise in the respiratory quotient, and that this is true, not only of dextrose, but also of lævulose.

The partial or complete inability of the tissues to utilize dextrose is not due to a general failure of the oxidizing power of the body. This is shown in many ways. In the diabetic organism benzol is oxidized to phenol, organic acids to carbonates, and fats to $CO_2$, and water just as in health. The most conclusive proof was afforded by the experiments upon respiratory exchange by Pettenkofer and Voit. They showed that the intake of oxygen, the output of $CO_2$, and the quantity of energy liberated per kilogramme of body weight,

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were the same in diabetic patients as in normal people; and the same has been found to be true of depancreatized dogs. The only abnormality in the respiratory exchange in diabetes is that the output of $CO_2$ is low in comparison with the intake of $O_2$. This is the cause of the low respiratory quotient, and is due to the inability of the body to utilize carbohydrates. Although diabetic patients liberate a normal quantity of energy in their bodies, they cannot obtain, of course, the same energy from a given quantity of food as a normal person does. In other words, a diabetic patient requires more food in order to cover the potential energy lost to his body as dextrose and acetone bodies in the urine. The magnitude of this loss can be estimated by calculating that 1 gramme of dextrose represents 4·1 calories, and 1 gramme of $\beta$-oxybutyric acid 4·5 calories. If an extra quantity of food is not given, the patient obtains energy from his own tissues, and wastes in consequence, and it is important to realize that the only cause of wasting in diabetes is starvation. Although a study of severe diabetes shows that muscles can obtain sufficient energy from fat and protein, it is well known that the utilization of dextrose is an important factor in the prevention of muscular fatigue, and this probably explains the muscular weakness associated with severe diabetes.

These are observations which help to give us a little insight into this inability of diabetic tissues to utilize dextrose. It has been found that depancreatized dogs and diabetic patients can still utilize substances which are closely related to dextrose and its immediate products of decomposition. Thus, *d*-gluconic acid, glycuronic acid, *d*-saccharic acid, mucic acid, succinic acid, etc., are oxidized in a normal way. From this we may conclude that the difficulty in diabetes is that the cells either have lost the power of combining with dextrose, or cannot carry out the initial step in the disruption of the dextrose molecule. In accordance with these two possibilities, we may imagine that the pancreatic hormone either is essential to the fixation of dextrose by protoplasm or activates a glycolytic ferment in the cells; and if the hormone is an amboceptor, it seems likely that these two possibilities are only different ways of stating the same thing. But we have seen reasons for adopting the first hypothesis in the case of the liver, and, provided that the internal secretion of the pancreas is a single substance, it seems likely that it would have the same function in relation to the protoplasm of different cells. And, further, as we shall see, unless we adopt this hypothesis, it is impossible to explain the useless overproduction of dextrose in diabetes, because if dextrose became attached to protoplasm, but could not be dealt with further, the affinities of the cells for dextrose and their demand for it would be permanently satisfied. We may therefore conclude as a working hypothesis that the pancreatic hormone is concerned in attaching dextrose to protoplasm, and that in its absence, the cells cannot

take up dextrose from the blood, and therefore can neither store it as glycogen nor obtain energy from it.

It is probable that fat is formed from carbohydrates by the synthesis of the products of decomposition of dextrose. If in diabetes the cells have lost the power of decomposing dextrose, it follows that they will at the same time have lost, and will prevent other cells from having, the power of storing carbohydrate as fat. This certainly seems to be the case in patients and animals suffering from severe diabetes. Not only do they not store as fat the dextrose which they cannot utilize, but they readily lose what fat they have.

3. **The Source of the Dextrose.**—When a patient suffering from severe diabetes is given a strict diabetic diet instead of ordinary food, there is a great fall in the excretion of dextrose ; but glycosuria still continues. The dextrose in this last case must be manufactured in the body from protein or fat, or from both.

The origin of dextrose from protein, as we have seen, is not proven scientifically, but we may safely assume that it takes place. If all the carbon in protein were converted into dextrose, the ratio D : N would be about 7 ; but all the carbon of protein is not so converted, and a D : N ratio of not more than about 3 is observed in experimental pancreatic diabetes during starvation. When such an animal is given protein free of glucosamine, the excretion of both dextrose and nitrogen is increased, and the ratio is unaltered. This fact suggests that the dextrose and nitrogen had a common source. And we believe that when protein in food undergoes deamidisation during absorption, a fixed proportion of the carbon contained in the simple fatty acids is synthesized in the diabetic organism and excreted as dextrose ; and the same must be true during the disintegration of tissue protein, because the ratio D : N is not altered by complete starvation. In the most severe cases of human diabetes, when the patient is eating a diet as nearly free from carbohydrates as possible, the ratio D : N is often higher than 3, and may be even higher than 7. This must be due to one of two things : either the diet does contain carbohydrate in excess of the patient's power of assimilation, or dextrose is being obtained from fat. Of course no diabetic diet is absolutely free from carbohydrates, but the presence in it of minimal quantities of carbohydrate will not explain the excretion of large quantities of dextrose when the ratio D : N is 12. We must therefore conclude that dextrose can be derived from fat as well as from protein.

It has been already stated that protein food increases the dextrose as well as the nitrogen in the urine ; but fat in the food behaves differently, and does not increase the glycosuria. Fat, unlike protein, passes into the circulation unaltered, and is stored unless it is needed by the tissues ; in other words, the amount of fat katabolized depends upon the needs of the tissues, and not upon the quantity eaten. Consequently there is no reason in diabetes why an

increased excretion of dextrose should follow an increased eating of fat, and it does not. Glycerine behaves differently; it can be synthesized into glycogen in normal animals, and in diabetic patients increases the glycosuria.

4. **The Overproduction of Dextrose.** — In the normal body carbohydrate food is stored as glycogen and fat. The tissues during activity call upon the store of glycogen, and when this store is exhausted dextrose is synthesized from fat or protein in accordance with the demands of the active cells. We do not know how these processes are regulated and how the cells make their needs felt. It is often assumed that, when the tissues are oxidizing dextrose, the abstraction of dextrose from the blood is itself the stimulus to other cells to liberate more dextrose into circulation. This simple and obvious explanation, however, is incompatible with the fact that in severe diabetes there may be an enormous overproduction of dextrose in the presence of great hyperglycæmia. It is possible that the stimulus is a chemical one, and that the products of the activity of cells circulating in the blood lead to an increased formation of dextrose.

In diabetes the glycogenic function of the liver is impaired, and alimentary glycosuria must result. In the mild type of the disease, when carbohydrate food is given, some of it is utilized by the tissues, some of it is stored as glycogen, or fat, and the remainder is excreted; and when a diet free from carbohydrate is eaten, the tissues manufacture dextrose from fat and protein only as it is required, and the glycosuria ceases. In the severe form of the disease, however, the glycosuria continues although no carbohydrate food is taken. In fact, the body deliberately manufactures dextrose which cannot be utilized, and it is this useless and often enormous overproduction of sugar which is one of the most surprising features of the condition. It is probable that the dextrose is synthesized from the products of the disintegration of fat and protein. These simple substances contain the same energy as the original fat and protein, and what we have to explain is why the body should synthesize these into dextrose instead of oxidizing them as they are. It is necessary to imagine that the cells of the body are in a condition of acute carbohydrate starvation in spite of the hyperglycæmia, that they are constantly crying out for dextrose, and that in response to this call dextrose is continuously manufactured, although there is no possibility of its being utilized. If, as we believe, the cells of the body have lost the power of taking up dextrose from the blood, they must be in a condition of acute carbohydrate starvation, and the overproduction of dextrose is a necessary consequence of their inability to combine with this form of food. In fact, the overproduction of dextrose from fat and protein is secondary, and is never a primary cause of diabetes. When present, it produces a continuous excretion of sugar apart

from the alimentary glycosuria observed after carbohydrate meals.

5. **The Power of Assimilation.**—It is usual in diabetes to apply this term to the maximal amount of carbohydrate food which the patient can absorb without any of it being excreted in the urine; and it is usually assumed that this quantity of carbohydrate has been stored or oxidized in the body. In cases of the mild type whose glycosuria has been stopped by dieting, it is obvious that all carbohydrate added to the food and absorbed which does not reappear in the urine must have been either utilized or stored. But the position is wholly different in cases of the severe type. In them the usual method of ascertaining the power of assimilation is to get their excretion of dextrose fairly uniform, if possible—say 50 grammes a day—on a constant diet, and then to add a known quantity of carbohydrate—say 30 grammes. If the corresponding urine contains 65 grammes of dextrose, the power of assimilation is said to be 15, and it is supposed that the tissues have utilized this quantity of dextrose. But in this line of argument there is a serious fallacy. If 100 grammes, instead of 30 grammes, of added carbohydrate are given to the same patient, it may be found that the quantity of dextrose excreted is very little greater than before, and that now 80 grammes instead of 15 grammes of carbohydrate have been assimilated; and at the same time it will be found that the total nitrogen in the urine is diminished. This result is open to two very different interpretations. We may say that 80 grammes of dextrose have been oxidized in the body, and have therefore caused a sparing of protein and fat. Such an interpretation is possible in the less advanced cases in which carbohydrate food still raises the respiratory quotient, and in them it may be wholly or in part true; but it is manifestly untrue in cases in which the respiratory quotient is no longer affected by carbohydrate food, and yet such cases give the same result. In them it is not possible that the dextrose has been oxidized, and unlikely that it has been stored; and we must imagine that the extra sugar from the food circulating in the blood has exerted by its mass influence a restraining effect upon the overproduction of dextrose from protein and fat. In fact, the term "power of assimilation" is used to cover two different methods of sparing protein and fat; one is sparing by the oxidation of dextrose, and the other is sparing by the accumulation of dextrose. It is possible to distinguish between the two only by estimating the total metabolism, including the respiratory exchange.

The power of diabetic tissues to utilize dextrose depends, as we have seen, primarily upon the supply of the pancreatic hormone. But there are other factors which may improve or impair this power temporarily or permanently, and of these the most common is hyperglycæmia. There can be no doubt that the hyperglycæmia is not only the immediate cause of most of the symptoms and

complications of diabetes, but leads automatically to a decrease in the power of assimilating carbohydrates. It would be hard to believe that such an excess of dextrose as is often present would have no effect upon cells, and, although it is not known how the effect is produced, there is such an obvious clinical connection between the degree of the hyperglycæmia and the power of assimilation that the fact cannot be doubted.

Another group of harmful substances are the general anæsthetics, especially chloroform, and the toxins of pathogenic bacteria. The relation of an infection and fever to glycosuria is by no means simple and constant. In a fevered patient otherwise healthy the glycogen in the liver and muscles is greatly reduced, probably because large quantities of dextrose are being utilized in the tissues; and in diabetic animals and patients with fever a diminished excretion of sugar has been observed. In this connection it is necessary to remember that in fever the food is generally changed very greatly, both in quantity and quality. But specific fevers often have an exactly opposite effect. In non-diabetic patients a temporary alimentary glycosuria may be produced, possibly, by direct injury to the cells of the liver and pancreas. In diabetes, for the same reasons a temporary or permanent increase in glycosuria may be produced, and in addition the increased metabolism associated with fever may lead to an increased overproduction of dextrose from protein and fat.

Lastly there are the intermediate products of metabolism which are concerned in the production of diabetic acidosis and coma. A too rigid diabetic diet, which favours greatly the formation of these bodies, may lead to a slow and continuous decrease of the assimilating power, whilst the administration of alkalies, which increases their elimination, has an opposite effect. So much is this the case that a patient whose respiratory quotient is not influenced by carbohydrate food may regain, after taking alkalies, such power of oxidizing dextrose that his respiratory quotient is raised by carbohydrates in his food.

6. **The Origin of the Acetone Bodies.**—The natural termination of all severe and progressive cases of diabetes is in coma, and we must now consider the formation of the acetone bodies and the other metabolic changes which lead up to this condition. The mother substance of the acetone bodies is $\beta$-oxybutyric acid, which by oxidation, yields aceto-acetic acid, and this in turn, by the loss of $CO_2$, forms acetone. Of these three bodies, acetone alone is excreted by a healthy person eating an ordinary mixed diet, and the combined daily excretion by the kidneys and lungs is about 0·1 gramme. But the term "acetonuria" is applied only when an abnormally large quantity of acetone is excreted in the urine.

In healthy persons there are a large number of conditions in which acetonuria and an excretion of the other acetone bodies may be

developed. Such conditions are the absence of carbohydrate from the diet, starvation, fevers, diseases of the alimentary canal, severe vomiting from whatever cause, anæsthesia, etc. The total excretion of acetone bodies may be very large, and amount to 50 to 100 grammes a day, reckoned as β-oxybutyric acid. The one factor which is common to all these conditions is a reduction in the quantity of carbohydrate available for utilization by the tissues. This is proved by the fact that in every case the excretion of acetone bodies can be reduced to normal in a few days by giving 50 grammes of starch or 100 grammes of lactose, cane-sugar, or dextrose. A similar but less marked effect is produced by large quantities of protein food, because of the carbohydrate which can be derived from its products of decomposition. In severe diabetes the excretion of acetone bodies is increased because, although large quantities of carbohydrate are available, the power of the tissues to utilize dextrose is impaired.

The source of the acetone bodies is still uncertain. They might be derived from carbohydrates, but this can hardly be an important source, because it is a diminution of carbohydrate metabolism which causes acetonuria. There can be very little doubt that the acetone bodies can be produced in the body from both protein and fat. It has been shown that the liver can form acetone from alanin and other simple protein derivatives. During the katabolism of fat we imagine that butyric acid is formed, and that this undergoes β-oxidation, with the formation of β-oxybutyric acid. Accordingly, we find in severe diabetes that the addition to the food of butyric acid or of butter, which contains large quantities of the lower fatty acids, increases considerably the excretion of acetone bodies ; but that oils and animal fats, which contain but little of the lower fatty acids, have much less effect.

Although β-oxybutyric acid is a normal intermediate product of metabolism, which is produced possibly on a large scale, it is not found in normal urine, and therefore all of it must be oxidized. There are good reasons for thinking that the line of oxidation of this substance into acetone is one which takes place only to a very limited extent in normal metabolism. For it has been found that acetone given by the mouth can be oxidized no more in the normal than in the diabetic organism, and is excreted unchanged by the kidneys and lungs ; but that β-oxybutyric acid does not produce acetonuria in normal men, although it does in cases of severe diabetes. The main line of oxidation of β-oxybutyric acid in normal metabolism appears to be through acetic aldehyde into acetic acid, and so into simpler compounds. It is therefore clear that in severe diabetes and other conditions of carbohydrate starvation the further oxidation of this acid not only partly fails, but also is diverted in abnormal quantities along an unusual line. No satisfactory explanation has been given of why carbohydrate starvation should lead

to a perversion and failure in the oxidation of this particular substance, and not of others at the same time.

In diabetes there are many indications that the main source of the acetone bodies is fat, and not proteins. For instance, there is not necessarily any parallelism between the total excretions of acetone bodies and nitrogen; and, further, Magnus-Levy has observed a case of diabetic coma in which more β-oxybutyric acid was excreted than could have been derived from the protein katabolized. But there is no evidence that the acetone bodies arise solely from fat, and not from proteins at all. And since they come from fatty acids which can be derived theoretically from protein just as well as from fat, it seems reasonable to adopt the view that they do have a double source of origin, and that the relative quantities derived from the two sources will vary with circumstances.

A consideration of the origin of the acetone bodies indicates that the quantity of them formed in any given case of severe diabetes will depend upon several factors: first, upon the power of utilizing carbohydrates—that is, upon the severity of the pancreatic disease; secondly, upon the diet—that is, upon the relative quantities of carbohydrate, fat, and protein, and upon the nature of the fats which it contains; and, thirdly, upon how far the diet covers the energy expended by the body and prevents starvation. The relation between the quantity of carbohydrate in the food and of the acetone bodies excreted is of great practical importance, and is at first sight peculiar, in that either an increase or decrease of carbohydrate may, according to circumstances, lead to a larger or smaller excretion of these bodies. A restriction of the carbohydrate may cause either an immediate increase by necessitating a greater katabolism of fat, or an ultimate diminution by improving the power of the tissues to utilize dextrose. An addition of carbohydrate to the food may produce a diminished excretion by sparing fat either by the oxidation of dextrose or by the mass influence of an increased hyperglycæmia; it may also cause ultimately an increased excretion of the acetone bodies by slowly impairing the assimilating power of the tissues. The exact effect produced in any given patient will depend chiefly upon the severity of the diabetes, and whether the quantity of carbohydrate given is within or beyond his power of assimilation.

According to the quantity and kind of acetone body excreted on a standard diet containing about 50 to 70 grammes of starch, it is possible to divide severe diabetes into three stages. In the first stage are those cases which excrete acetone alone, and in quantities which vary from the normal 0·05 gramme to 0·5 gramme a day. Such cases retain considerable power of utilizing carbohydrates. When carbohydrate food is withdrawn, the excretion of acetone is increased, and small quantities of diacetic and β-oxybutyric acids appear, just as they would in health. In the course of a week or

two the organism becomes accustomed to the altered diet, the diacetic and β-oxybutyric acids disappear, and the excretion of acetone falls. The second stage is marked by the constant appearance of diacetic acid in the urine, and this always takes place when the excretion of acetone is more than about 0·5 gramme a day. Patients in this stage still retain some power of utilizing carbohydrates, and their urine may even be freed from sugar if the quantity of protein eaten is restricted occasionally as well as carbohydrates eliminated from their diet. A strict diabetic diet causes a much greater rise in the excretion of the acetone bodies. If the rigid diet is continued, some cases in the course of weeks slowly become accustomed to the diet, and the excretion of these substances gradually decreases. Other cases show but little improvement in this respect. The third stage begins when β-oxybutyric acid is always present in the urine, and this is so when more than about 1 gramme of acetone is excreted in the day. However severe the case may be, the combined excretion of acetone and diacetic acid rarely exceeds 5 grammes; the β-oxybutyric acid begins to preponderate over the other two, and may amount to 100 grammes or more in the day. Cases in this stage show little or no power of utilizing carbohydrates, and the more this is so, the less is the influence of carbohydrate food upon the excretion of the acetone bodies; but even in these cases large quantities of carbohydrate food may reduce somewhat their excretion. A rigid diabetic diet increases the output of acetone bodies enormously. Some patients in the course of a week or fortnight become accustomed to the diet; others do not, and develop diabetic coma.

7. **The Genesis of Diabetic Coma.** — We have seen that in the metabolism of severe diabetes certain organic acids cease to be oxidized in the body, and that the more severe the disease the greater is this failure of oxidation. These acids could not be allowed to exist in the fluids of the body uncombined with a base, and it is necessary to consider how the base is supplied in diabetes. It is impossible, however, to understand this until we have considered briefly the relation of acids and bases in the normal body.

We may start from the axiom that it is essential to the normal working of cells that the ratio between the H and —OH ionic concentrations of tissue fluids should be maintained within normal limits. For this purpose it is necessary that the inorganic and organic acids should be properly balanced by the inorganic and organic bases. The inorganic acids and bases are introduced into or manufactured in the body from the food; but the organic acids and bases may be regarded as being formed in the body, and constituting the means by which the body regulates variations in the inorganic acids and bases. An examination of the urine will show in any given case by what means the acids and bases as a whole have been made to balance. Many organic acids are formed

in normal metabolism, and can be used for this purpose. The chief organic base is $NH_3$, which is split off in the breaking up of protein in the alimentary canal and tissues. When $NH_3$ combines with an acid, it is not converted by the liver into urea, but is excreted unaltered in the urine.

Various diets after being oxidized in the body yield very different quantities of inorganic acids and bases. A vegetable diet gives an excess of inorganic bases over acids. On the other hand, an ordinary mixed diet yields an excess of inorganic acids over bases, and this is still more so in the case of a diet composed largely of meat and fat, or during starvation, when the body is using up fat and protein and taking in no base. In the urine corresponding to an ordinary mixed diet the excess of inorganic acids over bases is considerable, the quantity of organic acid is very small, the amount of $NH_3$ much more than covers the organic acids, and the net result is a urine of moderate acidity. The $NH_3$ in this case amounts to about 1 gramme a day, and its nitrogen is from 3 to 5 per cent. of the total nitrogen. If a man eating a mixed diet is given 10 grammes of sodium bicarbonate, the condition of his urine is altered; the inorganic bases are in excess of the acids; consequently the $NH_3$ is reduced, but never quite disappears, and the organic acids are increased, but never sufficiently to prevent the urine from being alkaline. When a healthy man is given a diet free from carbohydrates, marked changes are produced in the urine, and these are still greater if the food does not contain vegetables. The organic acids are increased, aceto-acetic and $\beta$-oxybutyric acids make their appearance, and in order to cover this increase of organic acids more $NH_3$ is used, and a greater proportion of the total nitrogen in the urine is excreted as $NH_3$.

The term "acidosis" is applied to the condition in which abnormal quantities of organic acids fail to be oxidized by the tissues; and in order to neutralize the organic acids $NH_3$ is used, and therefore an increased percentage of the total nitrogen is excreted in the urine as $NH_3$. There is no evidence that acidosis leads to an increased katabolism of protein, and so to a greater quantity of $NH_3$ being available for neutralizing organic acid. The truth is that a very variable proportion of whatever quantity of $NH_3$ is being liberated can be taken for this purpose; in other words, the quantity of $NH_3$ available depends, not upon the need for base, but upon the quantity of protein which is being metabolized—that is, upon the diet. Besides $NH_3$ the body possesses a store of fixed inorganic base, which in case of need can be used to neutralize acids. The term "acidosis" must not be taken to imply that the body is being poisoned by acid—in other words, that the normal ratio between the H and —OH ionic concentrations of the tissue fluids is being disturbed. An acidosis is a condition of potential acid intoxication, which does not become operative until the body

can provide no longer the necessary base; and this point in an acidosis may not be reached for weeks, or even for years.

The less severe cases of diabetes, which secrete acetone alone and no abnormal organic acid, react, as we have seen, more or less like healthy people to a diabetic diet, and show only a transient acidosis. In the more advanced cases, which always excrete $\beta$-oxybutyric and aceto-acetic acids, acidosis is always present, and may continue for years without causing serious symptoms, provided that an appropriate diet is given. The acidosis is increased greatly when the patient is given a diabetic diet. The excretion of organic acids rises so rapidly that they are scarcely covered by the urinary $NH_3$, and at the same time the excess of inorganic acids over bases is much lower than is normal for the diet, because the body is being obliged to use its store of fixed base to neutralize acids. If this increase of acidosis is sufficiently great, the patient may pass into diabetic coma in the course of a week. And we have now to consider what is the connection between the acidosis and the onset of coma.

There are several points connected with the neutralization of organic acids in the body which must be touched upon, although they are most imperfectly understood. It is not obvious why $NH_3$ is not used more extensively than it is. The maximal excretion observed in man is about 10 grammes in a day, but in cases of diabetes passing into coma it may not reach 5 grammes, although protein is being metabolized in quantities sufficient to provide a great deal more. Again, the nitrogen excreted as $NH_3$ scarcely ever constitutes more than about 40 per cent. of the total nitrogen, and may be very much less even in cases of diabetic coma. When we remember that 1 gramme $NH_3$ will neutralize only 6 grammes $\beta$-oxybutyric acid, we see how insufficient this supply of base may be.

When the body has been exposed to a sufficient acidosis, the so-called "alkalinity" of the blood begins to fall. Numerous methods of estimating the "alkalinity" of the blood, plasma, or serum, have been devised; but, unfortunately, it is impossible to compare the results obtained by most of them.

The *reaction* of normal blood is really neutral—that is to say, the ratio of the concentrations of H and —OH ions is the same as that of distilled water. The limits of the relative concentrations of these ions within which the life of protoplasm is possible are very narrow; and so much is this the case that these limits fall well within the experimental errors of any known method of estimating directly these ionic concentrations. Consequently, the statement that in the blood of diabetic coma the concentration of —OH ions is low, but normal in relation to that of the H ions, is of no real value, and does not prove that diabetic coma is not a poisoning by H ions or acid intoxication. Although distilled water and blood

have the same reaction, their neutrality is affected very differently by additions of acids and alkalies. The slightest addition of acid or alkali to distilled water upsets the relative ionic concentrations enormously, and therefore alters the reaction of the fluid. But in the case of blood many times greater quantities of acids or alkalies may be added without changing its reaction. This power of withstanding additions of acids and alkalies has been termed *reactivity*, and it is due to the inorganic salts, such as bicarbonates and primary and secondary phosphates of the alkali metals, and to the proteins which are capable of acting as feebly dissociated acids and bases. Blood, therefore, is not only always neutral, but also has a very stable neutrality, due to the long range of reactivity given to it by certain of its inorganic and organic constituents. This is undoubtedly true also of all body and tissue fluids. A long range of reactivity is essential to protoplasmic activity, for during metabolism $CO_2$ and other acid substances are produced which would otherwise cause a rise in the concentration of H ions, and by altering the reaction make it impossible for protoplasm to function in a normal way and rapidly kill it.

In diabetic patients the alkaline reactivity of the serum, as determined by Wright's method, does not fall materially until they are on the verge of coma. At the same time the quantity of $CO_2$ in the venous blood is found to be reduced, and as the condition progresses little or no food is eaten, the total respiratory exchange diminishes, the excretion of dextrose, nitrogen, and the acetone bodies, falls rapidly, and the whole metabolic activity of the body appears to fail. Much attention has been paid to the diminution of $CO_2$ in the venous blood in diabetic coma. We know that the power of the blood to take up $CO_2$ from the tissues depends largely upon the inorganic bases in the plasma; it has therefore been suggested that this coma is a narcosis by $CO_2$, caused by the reduced "alkalinity" of the plasma. There are, however, the following fatal objections to this view: There is no parallelism between the reduction of "alkalinity" and the $CO_2$ in the blood. Further, by bandaging the arm before the blood is withdrawn from the vein, it is possible to raise the quantity of $CO_2$ up to, or even above, the normal. This proves that blood can still take up a normal quantity of $CO_2$ when the alkalinity of the plasma is reduced, and we know that when $CO_2$ is bubbled through blood alkali leaves the corpuscles and passes into the plasma. The reduction of $CO_2$ in the blood in diabetic coma has been shown to be due to the greater depth of the respirations. The increased ventilation pumps $CO_2$ at a greater rate than normal out of the blood and tissues. This process begins some days before the air hunger is clinically obvious. It has been shown in animals that a prolonged hyperpnœa of itself produces symptoms—namely, imperfect consciousness, rapid action of the heart, and a condition like that of surgical shock. It is

possible, therefore, that some of the symptoms in diabetic coma are secondary to the prolonged hyperpnœa; but whether this is so or not, it is still necessary to explain the nature of the stimulus to the respiratory centre which starts the process. The only suggestion which can be offered is that the reduced alkaline reactivity of the cells of this centre makes them highly susceptible to the action of an acid like $CO_2$, which is their normal stimulus.

There are, however, difficulties in believing that diabetic coma is nothing but an acid intoxication due to a reduction of alkaline reactivity, which in turn is caused by a diminution of certain inorganic basic constituents of the body fluids. For instance, an equally great reduction of alkaline reactivity of the serum may occur for a short time, as in scurvy, without producing similar serious symptoms. Efforts therefore have been made to show that $\beta$-oxybutyric acid has specific toxic effects apart from its action as an acid. These experiments, however, failed to demonstrate this. There might be other toxic substances concerned, but if so, we know nothing of them. Again, there is the difficulty that patients develop coma in spite of a preceding treatment by alkalies. We have seen that the normal body responds to the administration of alkalies by an increased production of organic acids, that none of these are excreted as acetone bodies, and that 10 grammes of sodium bicarbonate makes the urine alkaline and nearly free from $NH_3$. The less severe cases of diabetes react to alkalies more or less like normal persons, but in cases of severe diabetes, which are within measurable distance of diabetic coma, alkalies cause an increased excretion of acetone bodies which may be enormous. Some observers look upon this excretion as due to an increased formation resulting from the alkali, but we cannot agree with this view for the following reasons: The tissues post mortem may contain large quantities of $\beta$-oxybutyric acid, and this fact suggests that the elimination of this substance does not keep pace with its formation. Further, huge quantities of inorganic base may have to be given before the excretion of $NH_3$ is reduced to normal. Thus, a patient took 84 grammes of sodium bicarbonate daily for a month before the excretion of $NH_3$ fell to a normal value, and at the end of the time his urine had not become alkaline. It seems, therefore, reasonable to believe that in the terminal stages of diabetes there is a retention of $\beta$-oxybutyric acid within the cells which have produced it.

We must look to changes within cells, and not in the blood, for the ultimate explanation of diabetic coma. It is obvious that the production of an acid in abnormal quantity within a cell might produce toxic symptoms, whereas the same acid given by the mouth, or even directly into the circulation, might produce none. And in the same way in regard to the administration of alkalies. Although it is true that alkalies given by the mouth rapidly restore

the alkaline reactivity of the plasma to normal, it is pretty clear that the same change may not take place within cells with the same ease and rapidity. Alkalies certainly appear to have more effect in the treatment of diabetic coma which has been brought on acutely by a sudden and recent restriction of diet than when there has been a long-preceding and severe acidosis. Although it is clear that we do not understand completely the determining cause of the onset of diabetic coma, the only useful hypothesis at present is that the coma is due to a change in the reactivity of cells produced by the acidosis.

8. **Lipæmia.**—Two distinct conditions have been included in this term. In the first case, the material which gives the plasma or serum an obviously milky appearance is neutral fat. It is soluble in ether, gives the ordinary staining reactions for fat, rises to the top like cream, and may be separated by a centrifuge. Normal blood contains about 1 per cent. of fat; in diabetes the quantity may be normal or increased up to 10 per cent. or more. In severe diabetes fat in large quantities must be transported about the body; for not only does the food contain much fat, but fat is also being withdrawn from the subcutaneous and other tissues, and passed to the liver in order to undergo the preparatory changes necessary before it can be utilized by the working tissues. But this can hardly be the whole explanation of this kind of diabetic lipæmia; for in acute starvation and in poisoning by phosphorus an equally great transportation of fatty material takes place, and yet the blood does not contain nearly as much neutral fat as it may do in severe diabetes. In fact, neutral fat reaching the blood in the chyle rapidly disappears as such; it is changed by some means into some compound of fatty acid soluble in the blood, and in this state it passes in and out of fat cells, and is in the main transported about the body. It has been suggested, therefore, that the process of lipolysis may be impaired in severe diabetes, so that fatty material has to be transported largely as neutral fat.

The second and more frequent variety of lipæmia is a condition in which the milkiness of the plasma is not due to neutral fat. The material in question does not stain like fat, is insoluble in ether, does not rise to the surface, it is very finely granular and amorphous, and cannot be separated by a centrifuge. Chemically it consists of fatty acid partly free and partly in combination with cholesterin. There is also a considerable increase of lecithin in this blood. This kind of lipæmia is found only in severe diabetes. It may be so marked as to give the blood when drawn the appearance of crushed strawberries and cream, and may even be recognizable in the retinal vessels during life. It may be so slight, however, as to be noticeable only when the plasma or serum have separated. In one case as compared with another there is no connection between the lipæmia and the severity of the diabetes; but in any given

case of lipæmia there is a connection between the degree of the lipæmia and the progress of the case. Although this lipæmia is common in the more advanced cases of severe diabetes, it may be absent altogether, even in diabetic coma. A similar lipæmia has been reported in one case of sarcoma of the pancreas without diabetes. The analysis of this lipoid material suggests that the fatty acid liberated for the purpose of transportation has not been combined in the usual way, and so has become insoluble in the plasma.

9. **What Part of the Pancreas produces the Internal Secretion?** —Morbid histology shows that the pancreas can undergo considerable change without causing diabetes. It is therefore impossible to say what proportion of diabetic cases is of pancreatic origin until we decide what part of the pancreas produces the internal secretion. There are two possibilities: the hormone might be produced either by the islets alone or by both acini and islets. Unfortunately, there is an anatomical difficulty in deciding the question by experiment, because in all vertebrates down to the Teleostean fishes the islets are embedded in the acinar tissue, and cannot be removed separately. Morbid histology has failed to decide the question. The pathological material recorded in literature has been collected and reviewed both by Sauerbeck and by Herxheimer, and they come to diametrically opposite conclusions.

The view that the hormone is provided only by the islets is based upon the following considerations and observations: In the first place it is held that the islets are permanent and distinct anatomical structures, richly supplied with bloodvessels and unconnected with the ducts of the pancreas. And in the second place it is said that, in disease of the pancreas, diabetes is not produced unless the islets are included in the pathological change. The chief experimental evidence in favour of this view is the results obtained by ligaturing the pancreatic duct. After this procedure no diabetes follows; the acini are completely destroyed, and replaced by fibrous tissue in which healthy-looking islets are embedded. An exactly similar condition has been recorded in a man who was not suffering from diabetes, and whose pancreas was shown not to contain a trace of acinar tissue. This observation shows that tissue with the structure of islets can provide enough internal secretion to prevent diabetes, but it does not prove that the islets are the only part of the pancreas which produces the hormone. Further, there is grave reason to doubt whether the islets found embedded in the fibrous tissue are the unaffected and surviving islets of the normal pancreas. Many of them are of great size and many times larger than a normal islet. Again, Dale has found that ligature of the duct destroys the existing islets and acini equally, and that the islets found in the sclerosed pancreas are a new formation from acinar tissue. A similar conversion is brought

about by severe inanition and by exhausting the gland by injections of secretin. Although Dale's results have been denied, they have also been fully confirmed; they are in harmony with the embryonic formation of the islets, and are supported by Herxheimer's observations on the microscopical changes observed in "cirrhosis" of the pancreas in man. We may conclude, therefore, that, during slow destruction of the pancreas the acini can produce new islet tissue which is capable of providing the internal secretion necessary to prevent diabetes.

The above considerations do not tell us—and it is essential that we should know—whether the cells when arranged as acini also produce the hormone. Morbid histology does not throw much light on this question. The most common condition found is disease both of the islets and acini. But there are numerous cases of diabetes on record in which the acini alone are diseased—a condition which may be interpreted as showing either that the acini do produce the hormone or that the diabetes is not pancreatic.

On the whole it seems advisable to adopt the view that the internal secretion is produced both by the normal acini and by the normal islets. If this is admitted, then it follows that all cases of severe diabetes are probably of pancreatic origin. The reason for saying so is twofold. In the first place, changes in the pancreas are found in a great majority of cases of severe diabetes. And, in the second place, we know of no experimental means of producing a similar diabetes other than by removal of the pancreas. It follows, also, that many cases of mild diabetes are probably pancreatic; some of these cases die of intercurrent disease, and others progress into the severe form of the disease.

10. **Can Pancreatic Diabetes have an Intestinal Origin?**—There are cases of severe diabetes in which the pancreas and all other organs have been described as "normal" microscopically. Many of these cases are very severe and acute, and occur in young patients with a strong family history of diabetes. They are placed by Naunyn in a special class by themselves. It must be remembered, however, that no organ undergoes post mortem more rapid change than the pancreas, and that in most cases the organ is not sufficiently fresh to justify definite statements about the finer structure of the cells. It may even be doubted how far the granular atrophy of the acinar cells, which is described as the first stage in "cirrhosis" of the pancreas, is not a post-mortem change.

It is possible that there really are cases of severe diabetes in which the pancreas is normal, and if so, we should have to explain the diabetes as being due to a functional disturbance of the gland. The most obvious cause of such a disturbance would be the absence of the chemical stimulus which is necessary to make the pancreas turn out its internal secretion; for we imagine that during the digestion of carbohydrate a hormone with this property must

reach the pancreas from the intestine. Starling suggested that secretin might be the stimulus to the internal secretion of the pancreas, just as it is to the external secretion. And, in accordance with this idea, it has been claimed that some cases of severe diabetes can be cured or benefited by large doses of a secretin solution given by the mouth. This observation seems at first sight to be supported by the fact that in some cases of fatal diabetes prosecretin is either absent from the small intestine or greatly reduced in quantity. It has not been found possible to decide experimentally whether this absence of prosecretin is the cause or an effect of the diabetes, but it is probably an effect, and possibly the result of the prolonged acidosis. Further, the majority of observers who have treated patients with secretin given by the mouth, hypodermically, or even intravenously, have failed to observe any influence upon the glycosuria. In fact, we do not know that there are cases of pancreatic diabetes due to a functional disturbance of the pancreas of intestinal origin.

There are a few other experiments in connection with pancreatic diabetes which have such a direct bearing upon treatment that they may be briefly mentioned. Feeding animals and patients with raw pancreas improves the absorption of proteins and fats, but does not diminish the glycosuria. Islet tissue obtained from Teleostean fishes has no glycolytic action *in vitro*, and when administered by the mouth or hypodermically to diabetic patients has no marked effect upon the glycosuria. Intravenous injections of an extract of pig's pancreas, made according to Cohnheim's method, have been given to several cases of severe diabetes; and in one patient, who died a few months later of diabetic coma, the injections were continued every day for several weeks. No constant effect upon the glycosuria was observed. The injections are very unpleasant to the patient, because they produce instant flushing and headache, and sometimes symptoms which are clearly dangerous. The only known way to prevent or cure pancreatic diabetes is by grafting. The pancreas for this purpose must be from an animal of the same species; otherwise the graft would be rapidly destroyed by cytolysis. The grafts gradually atrophy, and would have to be renewed in order to prevent the diabetes.

### B. Some Other Changes in Carbohydrate Metabolism.

1. **The Excretion of Glycuronic Acid.**—Blood contains glycuronic acid which is excreted in the urine in combination with part of the phenol, indol, and skatol, which is formed in the alimentary canal. Glycuronic acid has been proved to be obtainable in the body from dextrose, and it must be looked upon as a normal intermediate product of carbohydrate metabolism. A small portion of the glycuronic acid formed in the body is excreted in the urine as

oxalic acid, and the remainder is completely oxidized, unless it becomes combined into a compound which resists further oxidation. Consequently, an increased formation of indol, phenol, etc., in the alimentary canal causes an increased excretion of these substances in combination with glycuronic acid. Alcohols and phenols capable of combining with glycuronic acid are formed in the body from many drugs, such as carbolic acid, chloral, acetone, naphthalin, antipyrin, camphor, and terpenes, and in this way cause an increased excretion of glycuronic acid. In all these cases it is clear that glycuronic acid, like ethereal sulphuric acid, combines with poisonous substances and prevents intoxication; and consequently the ethereal sulphates are increased in the urine at the same time as the compounds with glycuronic acid.

There are, however, cases in which the excretion of ethereal sulphates is decreased in proportion as that of glycuronic acid is increased. Such a condition has been observed in severe diabetes, after poisoning with CO or curare, and in cases of severe disturbance of the circulation or respiration. In all these conditions the greater excretion must depend upon an increase in the quantity of glycuronic acid to be eliminated. This increase can hardly be due to a failure of the power of the tissues to oxidize glycuronic acid, because we have already seen that diabetic patients can oxidize it completely when it is administered to them by mouth. At present it is impossible to say what a spontaneous increase of glycuronic acid in diabetic urine means.

2. **Maltosuria.**—It is probable that traces of maltose occur in normal blood and urine. Some observers have considered that this sugar is not maltose, but isomaltose. It seems likely, however, that it is maltose of which the osazone has been altered in shape and melting-point by the presence of other osazones.

An alimentary maltosuria is not known for certain to occur. In healthy people and in diabetic patients the maltase is always able to convert all the maltose into dextrose, and dextrose alone is found in the urine. It has been observed that chronic alcoholic patients may pass a sugar in their urine after taking beer, and it has been suggested that this is an alimentary maltosuria due to a deficiency of maltase.

Very few undoubted cases of spontaneous maltosuria have been observed. In some cases of severe diabetes, and sometimes after the removal of the pancreas in dogs, small quantities of maltose have been found in the urine, together with very much larger quantities of dextrose. In interstitial pancreatitis it is said that maltose alone may be found in the urine. Nevertheless it is impossible to say at present that spontaneous maltosuria is diagnostic of pancreatitis, because it has been observed in cases of diabetes in which pancreatic disease could not be demonstrated.

3. **Excretion of Polysaccharide Substances.**—Normal urine has been found to contain in a day about 0·15 gramme of a dextrin-like carbohydrate. In a few cases of diabetes this material has been found to be very considerably increased. The source and significance of this substance are unknown.

Traces of glycogen have been found in diabetic urine. It is well known that the renal epithelium in severe diabetes may contain large quantities of glycogen, which is probably the source of that in the urine.

4. **Lævulosuria.**—Alimentary lævulosuria may occur both in healthy people and in cases of diabetes when this sugar has been eaten in quantities too great for the patient to assimilate. It is common in disease of the liver when the patient has been fed with a sufficient quantity of lævulose, cane-sugar, or inulin. The alimentary lævulosuria which has been observed during eclampsia and after poisoning with thyroid extract is also probably of hepatic origin.

Another and very rare form of alimentary lævulosuria has been recorded. The patients have shown a pure lævulosuria, which has ceased directly lævulose or any sugar yielding it has been withdrawn from the diet. Further, the injection of phloridzin has caused, as in normal men, a secretion of dextrose, and not of lævulose. These facts prove that the lævulose in the urine is not manufactured from dextrose in the body, but is derived entirely from the good. A consideration of the degree of the lævulosuria suggests that the liver has not lost any of its power of storing lævulose as glycogen, but that the small proportion of lævulose, which is normally burnt up directly, escapes utilization in these patients, and is excreted in the urine.

Spontaneous lævulosuria is a comparatively rare condition, and has been described most frequently in connection with diabetes. In severe diabetes small quantities of lævulose, in addition to large quantities of dextrose, have not infrequently been recorded in the urine, even when the patient was eating no carbohydrate food. The presence of lævulosuria in these cases has been determined almost solely by the use of Selivanoff's reaction, and since it is doubtful how far this test is reliable in diabetic urine, it is uncertain whether lævulosuria is of such frequent occurrence in severe diabetes.

Another and apparently distinct variety of spontaneous lævulosuria has been described. The urine has contained both dextrose and lævulose, but the lævulose has been the principal sugar present. The lævulosuria is not alimentary, because the patients have behaved towards a dose of lævulose exactly like normal individuals. The administration of large quantities of dextrose by the mouth has generally been found to increase the excretion of both sugars to a greater or less extent. This result suggests that the lævulose

in the urine has been manufactured in the body from dextrose, and this idea is supported by the observation that an injection of phloridzin leads to an excretion of both sugars, whereas in normal people dextrose alone is passed out. Clinically these patients have been very few in number. They have shown polyuria, thirst, and other symptoms, associated with an excess of sugar in the blood, but none of the serious symptoms common in severe diabetes; and in all cases a carbohydrate-free diet has caused both sugars to disappear rapidly from the urine. These patients appear to suffer from an error of metabolism which is wholly different from ordinary diabetes. The pathology of the condition is not known, and, as in the case of diabetes, may not be the same in all cases.

5. **Lactosuria.** — Alimentary lactosuria can be produced with ease both in healthy people and diabetic patients. In pregnant women a comparatively small dose of lactose may suffice to cause the condition. The exact significance of this observation is uncertain. Lactosuria has been observed in breast-fed children suffering from gastro-enteritis, and in these cases is presumably due to a partial failure of the action of lactase. In a few of these children the urine has also contained galactose and dextrose.

Spontaneous lactosuria is known to occur only during pregnancy or lactation. In animals the excretion of the sugar is stopped at once by removal of the mammary glands. There can be no doubt that the condition is due to the absorption of lactose from the gland into the blood. A spontaneous lactosuria has been described in puerperal women when they were given large doses of glucose. It is probable that the glucose in these cases leads to an increased formation and absorption of lactose from the mammary glands.

Paul Bert and others have brought forward experimental evidence to show that a marked glycosuria occurs in animals who become pregnant after removal of the mammary glands. They believed that there was a hyperglycæmia of hepatic origin, and that the dextrose excreted in the urine would have been converted in an intact animal by the mammary gland into lactose. Recent repetitions of these experiments have failed entirely to confirm the occurrence of glycosuria under these circumstances; nevertheless a true glycosuria during pregnancy in otherwise healthy women is by no means rare.

6. **Pentosuria.**—The excretion of a five-carbon sugar in the urine is a rare but interesting condition. A pentose given by the mouth or injected subcutaneously is most imperfectly utilized in the body. Some of it is oxidized, as has been proved by the rise in the respiratory quotient; it may also lead indirectly to a formation of glycogen in the liver, but much of it is excreted unaltered. Alimentary pentosuria has been observed in healthy persons and in diabetic patients after they have eaten large quantities of certain fruits, such as apples, cherries, plums, etc., which contain *l*-arabinose.

Alimentary pentosuria can be produced more easily in diabetes than in health.

Spontaneous pentosuria has been observed in severe diabetes both in human beings and in starving dogs after removal of the pancreas. The nature and significance of the pentose excreted is unknown. The most interesting variety of spontaneous pentosuria is that which is found in people who are apparently in perfect health and show no other metabolic peculiarity. The condition is not accompanied by any symptoms or change in health; it is continuous and lifelong, and seems to be due to a change in carbohydrate metabolism which is hereditary and of no pathological importance. In fact, such a pentosuria is analogous to alkaptonuria or cystinuria.

Spontaneous pentosuria is independent of pentose in the food. The pentose found in the urine has generally been the optically inactive mixture of *d*-arabinose and *l*-arabinose. The quantity excreted may be far too great for it to have been derived from the xylose in nucleic acid. It must therefore be manufactured in the body, probably from galactose, and ultimately from dextrose.

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# CHAPTER XVIII

# GOUT

By I. WALKER HALL

Gout is a term which does not signify any doctrinal or nosological entity; it is simply a name for a number of pathological conditions in which a common symptom has suggested the action of a particular etiological factor. This symptom is the presence of an excess of uric acid in the blood and tissues.

The disease itself is chronic in type, but is characterized by paroxysmal outbursts; these paroxysms are accompanied by pyrexia and an inflammatory reaction.

When considering the pathology of gout, it is necessary to deal separately with the several phases of the disease. It will be an advantage, therefore, at once to set forth what is generally included by the clinician under the headings of Acute Gout, Chronic Gout, Irregular or Metastatic Gout.

**Acute Gout.**—For a few days a patient, generally about middle age, may have complained of slight dyspepsia, headache, nervous depression, or excitability. He goes to bed apparently well, but in the early hours of the morning he is awakened suddenly by excruciating pain in the metatarso-phalangeal joint of the great toe, or in the ankle, instep, heel, or knee. This is accompanied by a slight rise of temperature and shivering. Some hours later the pain abates and he perspires slightly. On examination, the painful joint is found to be swollen, the overlying skin is livid, red, œdematous and tender. During the day the pain subsides, but on each of the following eight to fourteen nights the pain returns, increases in severity, and subsides again the following morning. The redness attains its maximum intensity in twenty-four to thirty-six hours, and then fades. The œdema, on the contrary, continues to increase for six to eight days, and then disappears. Peri-articular swelling, however, remains, and the joint is permanently enlarged. Were the joint to be opened at this stage, it would be seen that the synovial membrane is injected and spongy, that the synovial fluid is turbid, scanty, contains polymorphonuclear leucocytes, and sometimes crystals of biurate of sodium. The cartilage cells show proliferative changes, and the matrix fibrillation; sodium biurate

crystals are being deposited close to the free edge. The patient's lungs and heart may appear quite sound, but the blood-pressure and the molecular concentration of the blood are increased after the attack, and the "filtrate nitrogen"* of the blood may be raised. Pyorrhœa alveolaris is often present, and intestinal putrefaction is indicated by an excess of urinary indican. The fæcal nitrogen is increased. Although clinical signs of renal trouble may be wanting, there are several significant changes in the urine. It is febrile in character, the urea and urobilin outputs are augmented; the acidity, ammonia and monoamino-acids are unaltered; the uric acid content is decreased before the attack, but is increased during the attack. Transient albuminuria is sometimes present.

**Chronic Gout.**—Such an acute attack may be the first and last. Frequently, however, a second attack is followed by others, and a condition of chronic gout ensues. The attack now clears up more slowly, and additional joints are involved. The deposition of urates is more marked, the synovial membranes undergo fibrosis, the cartilage and bone show hyperplasia, and the joint becomes permanently enlarged and deformed. In addition, uratic deposits appear in the form of subcutaneous nodules called "tophi," chiefly affecting the auricles of the external ear and the vicinities of joints. The repetition of the systemic changes occurring in the acute attacks is associated with the appearance of chronic vascular, alimentary, and renal lesions, and these complicate the condition.

Between the attacks there is an increased output of the total urinary and fæcal nitrogen. The uric acid excretion is maintained at a low physiological level. The blood contains uric acid in a form which allows of easy extraction. The red and white corpuscles are not altered quantitatively, but some leucocytes show perinuclear basophilic granulation, and large white cells of a degenerate type may make their appearance.

**Irregular Gout.**—When the gouty paroxysm is localized in tissues other than a joint, the condition is termed "irregular gout." When it occurs in the tonsil, pharynx, or parotid gland, it occasions intense congestion, œdema, and pain, while permanent thickening of the tissues may ensue. When it appears in the stomach and intestine, severe abdominal pain, vomiting, or marked derangement of the secretory and digestive functions, are produced. The trachea, bronchi, and lungs, may be affected in a similar manner, and urates may be deposited in the vocal cords, arytenoids, and the ligaments and joints. The circulatory system is sometimes attacked. Cardiac pain, syncope, or irritability, may occur, and phlebitis is common.

* The term "filtrate nitrogen" has replaced the older terms "extractive or non-proteid nitrogen." It included urea and nitrogenous extractives. Normally there are 25 to 35 milligrammes for 100 c.c. of blood serum, but in the acute attack of gout it may be increased to 35 to 75 milligrammes.

Migraine, neuritis and neuro-fibrositis, insomnia, mental depression, vertigo, and transient paraplegia, are some of the manifestations in the nervous system. In the genito-urinary system the deposits of urates occur in the kidney, while the ureter, bladder, and urethra, are irritated by the passage of scanty acid urine. Orchitis and epididymitis sometimes ensue. At a later stage organic renal disease sets in. Cutaneous eruptions are not uncommon, and uratic deposits have been demonstrated in these and in the sheaths of superficial nerve fibres.

**Retrocedent or Metastatic Gout.**—When a sudden subsidence of the attack in a gouty joint is succeeded by a paroxysm in one or more of the internal viscera, the condition is known as "retrocedent" or "metastatic" gout.

**Morbid Anatomy.**—At an autopsy upon a gouty subject the chief features are fibrosis and uratic deposits. Externally the smaller joints are deformed and tophaceous. The heart is usually enlarged, the left ventricle hypertrophied, the myocardium contains patches of fibrosis, the valves are thickened, and the aorta and coronary arteries are atheromatous. There is generalized arterio-sclerosis. The blood contains an excess of uric acid. Chronic bronchitis is often met with. Cirrhotic changes are generally demonstrable in the liver, pancreas, and kidney.

The cartilages and ligaments are streaked with white chalky masses; these masses are soluble in hydrochloric acid, and the solution yields whetstone crystals of uric acid on standing. Similar deposits occur in the form of flakes or stripes in the pyramids of the kidney. On microscopical examination urates may be demonstrated in almost all the tissues of the body.

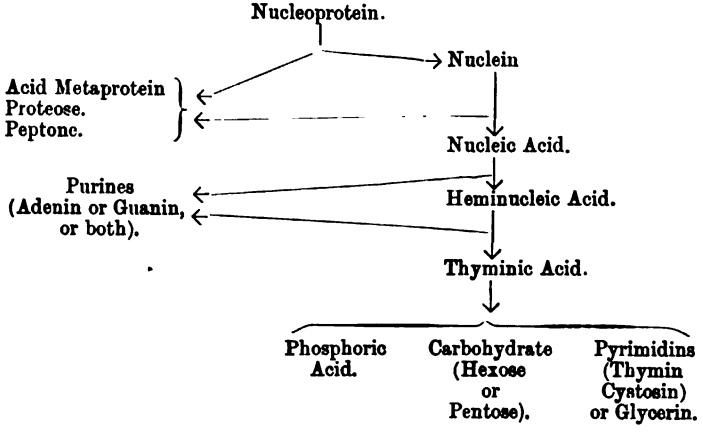
In gout, therefore, we have to do with a disease affecting the whole of the body tissues. Common to all the types is the appearance of uratic deposits and an excess of uric acid in the blood-stream, together with a low physiological level of nuclein metabolism. For many decades attention was focussed upon these two symptoms, and the disease was considered a "uric acid" disease. The presence of an excess of uric acid in the blood-stream, however, is not in itself sufficient to produce gout. In leukæmia, in pneumonia, and in suppuration, the blood contains a large amount of uric acid, but the patients do not become gouty; the uric acid is excreted by the kidney, and the blood-content regains its usual level; joint attacks are rare, and urates are not deposited in the tissues. In gout, therefore, there must be some other factor, or factors, than uric acid. A knowledge of such factors would solve many of the difficulties connected with the pathology and treatment of gout.

Before considering the metabolism of the gouty individual, it is well to review some of the recent work upon normal metabolism.

### The Normal Metabolism of Nucleins.

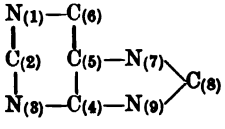
Of the formation of the normal nucleins of the body we know little. There is no evidence to show that nucleins present in the food are used for this purpose. Nuclein may be built up under conditions when an intake of nuclein is impossible. That there is a continuous synthesis of nuclein is very probable, but how this is brought about and what substances are used for the purpose is at present unexplained.

More is known of the breaking down of nuclein. While it is impossible to say that in the living tissues one and the same method always obtains, it is possible that the following scheme represents one way in which the process may be carried out:

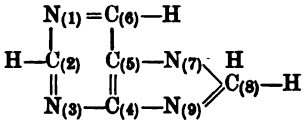



The term " breaking down " of nuclein does not necessarily imply a disintegration of nuclein. When a cell dies, its nucleus breaks up and its nucleic acid yields cleavage products, the amino- and oxy-purins. But nuclein metabolism goes on while the cell is living and active, and the excretion of nuclein cleavage products is necessary because the cells are fulfilling their functions, and a functional exchange of nuclear material is proceeding.

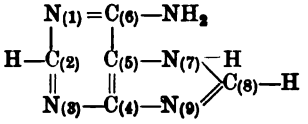
The work of Kossel and Emil Fischer has shown that the purin nucleus contains five atoms of carbon and four atoms of nitrogen arranged in double ring form:



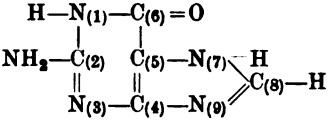
The synthetic purin has the following constitution :



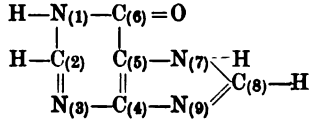
By substitution of an amino-group, adenin, or 6-amino-purin, is formed :



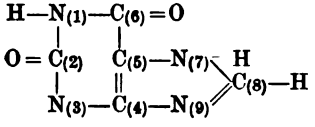
By substitution of an amino-group after oxidation, guanin, or 2-amino-6-oxypurin, is formed :



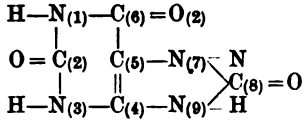
By oxidization of purin, hypoxanthin, or 6-oxypurin, appears :



By addition of a second atom of oxygen, xanthin, or 2·6-dioxypurin, is produced :



Further oxidization results in the appearance of uric acid, or 2·6·8-trioxypurin :



The addition of a methyl group results in the formation of methyl purins, which play a large part in therapy, such as theobromin, theophyllin, theocin, caffein, etc. When ingested these are chiefly excreted as methyl purins.

**The Source and Formation of Purin Bodies.**—Purin bodies may be most easily obtained from richly cellular organs, such as the thymus, spleen, liver, or testis. When portions of these organs are submitted to the prolonged action of hot dilute solution of a mineral acid,

adenin and guanin in large quantities, and xanthin and hypoxanthin in small quantities, are found. When muscular tissues are treated similarly, the result is a large percentage of hypoxanthin and xanthin and a smaller percentage of guanin and adenin. Uric acid cannot be extracted from human organs by such methods, although small quantities may be obtained from the spleens of certain animals.

There is every reason to believe that the amino-purins, adenin and guanin, are the primary products of breaking down of nucleic acid, and that the oxypurins, xanthin, hypoxanthin, and uric acid, are from a secondary oxidation; for if cell-rich animal or human tissues are minced and kept at body temperature in an incubator for one or two days under conditions which inhibit putrefactive changes, and at the same time insure a uniform supply of sterile air, analyses made at certain intervals show that amino-purins first appear, and that in turn the oxypurins (xanthin, hypoxanthin, and uric acid) are demonstrable. In the former instance heat and dilute acid were employed to break up the cell nucleins; in this method the cleavage appears to be due to the action of the following ferments:

1. Nuclease—a ferment which breaks down nucleinic acid and sets free the amino-purins adenin and guanin.

2. Deamidases—hydrolytic ferments, adenase and guanase, which liberate the amino-group and leads to the appearance of xanthin and hypoxanthin:

$$\underset{\text{Guanin}}{C_5H_5N_5O} + H_2O = \underset{\text{Xanthin}}{C_5H_4N_4O_2} + NH_3$$

$$\underset{\text{Adenin}}{C_5H_5N_5} + H_2O = \underset{\text{Hypoxanthin}}{C_5H_4N_4O} + NH_3$$

3. Oxidase—a ferment which oxidizes xanthin to hypoxanthin, and h ypoxanthin to uric acid.

$$\underset{\text{Hypoxanthin}}{C_5H_4N_4O} + O_2 = \underset{\text{Uric acid}}{C_5H_4N_4O_3}$$

These ferments are not present in all the tissues; oxidase, for instance, occurs in the spleen, lungs, liver, intestine, muscle, and kidneys, of oxen, while in dogs and cats it is less widely distributed.

Another ferment which causes uric acid to break up into simpler bodies has lately been isolated. It has been termed a "uricolytic" ferment. When uric acid is added to minced liver, muscle, or kidney, and kept at body temperature, a considerable portion of the uric acid is destroyed. Uricolysis seems to be carried out most efficiently by renal tissues.

Investigations carried out recently upon fœtal and human surviving tissues show that the results attained with animal tissues are fairly applicable to metabolism in man. Hence it may be premised that a part of the nuclein metabolism is carried on by ferment action, and consists of the production of amino- and oxy-purins.

from a mother-substance or from nucleic acid itself, and the subsequent partial breaking down of the tri-oxypurin, uric acid.*

So far the metabolism of nuclein has been considered without reference to the nuclein content of food. The relation of the nuclein, or purin contents, of the food to that of the tissues demands careful discussion. So long as the dietary consists of purin-free or purin-poor foods, such as milk, eggs, cheese, rice, bread, butter, or certain vegetables, only, the nuclein metabolism is but little affected. But when meat, fish, beer, pulses, oatmeal, etc., are taken, definite quantities of purin substances are introduced into the body, and require to be assimilated or excreted.

In this way the purins may be classed under two headings: the *exogenous*, derived from food nucleins; and the *endogenous*, derived from the nuclei of the actual working cells of the body. Both types of nuclein appear to yield uric acid as an intermediary product. Under normal conditions both types yield the uric acid in such a form that a portion is excreted easily by the kidney as uric acid, and a portion is broken up further to urea or to intermediate bodies. Since, however, only certain organs are able to build up or break down uric acid, the amino- and oxy-purins must be carried from their places of origin to the uric acid forming and destroying organs.

**The Transport of Purin Bodies.**—The blood and lymph are the natural means for transporting the purin compounds from one place to another. They act as carriers only—that is to say, they do not alter the form or quantity of the uric acid during its circulation. There are some who would contest this statement, but the weight of evidence is in favour of this passive action of the blood-stream.

On a nuclein-free diet normal blood does not yield any uric acid to the ordinary methods of extraction.

On an average mixed diet containing nucleins or amino- or oxy-purins, 0·8 to 1·0 milligramme of the tri-oxypurin (uric acid) may be obtained per 1,000 c.c. of blood. When the quantity exceeds this amount the condition is termed "uricæmia" or "uratæmia." This uricæmia is generally temporary in character. Thus, after a meal rich in nuclein material the uric acid content of the blood is much increased, and an *alimentary uricæmia* is produced. In leukæmia, in pneumonia before and after the crisis, and with X-ray treatment, there is marked activity and destruction of cell nuclei, and a consequent overproduction of endogenous purins; a *functional uricæmia* follows. In renal diseases and uræmia the secretion of urine is altered, and the blood is sometimes surcharged with uric acid owing to defective excretion; this is termed a

* It is held by some that a portion of the uric acid is synthetized from simpler substances, but the evidence supporting the contention is very slight. In any case, it is only claimed that a small amount may arise in this way.

*retention uricæmia.* In gout there is a uricæmia which persists when the diet is purin-free and when the kidneys do not afford any clinical signs of altered function; here the *uricæmia* is *permanent.*

*Temporary Uricæmias.*

Alimentary uricæmia, up to 12 milligrammes uric acid per 100 c.c. blood-serum.

Functional uricæmia (leukæmia), up to 22 milligrammes uric acid per 100 c.c. blood-serum.

Retention uricæmia: Chronic nephritis, up to 10 milligrammes uric acid per 100 c.c. blood-serum; uræmia, up to 16 milligrammes uric acid per 100 c.c. blood-serum.

With regard to the transport of purins in the blood and lymph streams, only a few facts are available. One part of uric acid is soluble in 1,000 parts of the blood-serum of oxen, a solubility thirty-five to forty-five times greater than in distilled water. This is not due to any excess of alkalinity in the blood-serum, for the blood-serum is normally neutral, and in the experiment which furnished these figures it was intentionally acidified. Blood-serum possesses the power of taking uric acid into solution, but loses this property when it is incubated at 37° C. for some hours. The addition of the uric acid does not alter the electrical conductivity of the serum. Already dissolved uric acid may be separated from the serum. Mechanical means, such as the centrifuge, suffices for the removal of a part of the uric acid, but a portion remains which requires special extraction methods. One part of the uric acid, therefore, is more firmly bound than the other. This is particularly so in uricæmia.

It is probable, therefore, that uric acid is carried in the blood-stream in some combination with organic material, and not in the form of a salt, or, as Taylor says, "it is difficult to conceive of a substance with such a low coefficient of solubility and constant of dissociation being combined with a kation like sodium to form an electrolyte in a complex fluid like blood, with its colloids, amphoteric substances, electrolytes, and large content of a gas with acid reaction." Taylor affirms it is quite certain that uric acid cannot circulate to any extent as a disodium urate (a strong alkaline salt) or as monosodium urate (a weak alkaline salt). A compound containing pyrimidin—thymic acid—has been suggested as one of the substances with which uric acid might form a firm compound; for the addition of thymic or nucleic acid to a solution containing uric acid and the purin bases hinders the precipitation of the purin bodies by ordinary methods. Whether or not such a combination is formed in the blood-stream is unknown; the compound has not yet been isolated, and a mixture, the sodium salt of $\alpha$-thymo-nucleic acid and uric acid, injected intravenously does not, in animal experiments, facilitate the excretion of uric acid.

There must be other organic compounds which can enter into the necessary combination, for the renal cells excrete more easily that moiety of uric acid which is "masked" during circulation in the blood-stream.

**The Excretion of Purin Bodies.**—The oxypurins—uric acid, xanthin, and hypoxanthin—are eliminated by the urine. Adenin, guanin, xanthin, hypoxanthin, and in some instances traces of uric acid, appear also in the fæces, but here they arise from the alimentary secretions, glandular cells lining the tract, bacteria, and unabsorbed food, and have little or nothing to do with the internal purin metabolism.

The urinary purins, as previously mentioned, are derived from two sources, the endogenous resulting from the activities of nuclear and cellular processes, the exogenous being derived from food. When the food does not contain purin-holding material, the daily total quantity of purins appearing in the urine is fairly constant for each individual, although variations due to nitrogenous intake, to illness, work, etc., may occur. There is a fairly well defined range of output with upper and lower physiological limits.

The daily total purin output comprises a large percentage of the tri-oxypurin, uric acid, and a small percentage of purin bases. The daily output of these two constituents varies much more than does the total purin output, so that the uric acid excretion cannot be taken alone as an index of the total purin metabolism.

Recently it has been shown that the hourly output of uric acid does not correspond to that of urea. The excretion of uric acid is unaffected by the periods of digestion and assimilation, reaches its highest point during the early hours of the day, and declines towards evening. During the night it continues to be excreted at a low level, and is unaffected by the use of diuretics. There is therefore no retention, the rate of output corresponding to the output of mental and bodily energies. Severe muscular exercise and the action of an hepatic and general stimulant, such as salicylic acid, causes a late rise in the amount of uric acid excretion and an early rise of purin bases output, but muscular rest does not lead to a diminution of the usual individual amount. Urea, on the other hand, is directly affected by the periods of digestion and assimilation, is low in the early morning, high after the last meal of the day, and responds promptly to the flushing action of diuretics (Leathes).

When purin-containing food is added to the dietary, there is a rise in the uric acid output, which follows somewhat the course of urea, and, although there are slight individual variations due to changes of habits, health, etc., about 40 to 60 per cent. of the purins of the ingested food appear in the urine. At one time these figures

were accepted as dogma, but of late it has been suggested that the increase in nitrogenous intake may have some effect on the functional activities of the cells, and thus increase the total purin output. There is also the possibility that some constituent of meat, sweet-bread, or nucleic acid, may act like a drug or catalyst, and intensify the endogenous purin metabolism. Future work must determine the accuracy or otherwise of these possibilities.

What has happened to the missing 60 to 40 per cent. of ingested purins? It has been shown that ferment action leads to uric acid formation and uric acid destruction in one and the same organ, and that the relative amounts of the di-oxypurins, and the tri-oxypurin uric acid vary with conditions of oxidization, the total purin output remaining fairly constant. It is permissible, therefore, to surmise that the missing purin has been broken down to simpler substances, since the most careful experimentation fails to disclose any retention of uric acid under normal conditions. So long as this holds good for exogenous purins, it is fair to argue that similar conditions obtain for endogenous purins, and to regard the urinary output as representing a proportion of the total endogenous uric acid only. What this proportion is it is impossible to say, but it is probable that on the one hand the amount varies for each individual, and on the other hand that the changes of endogenous purins may be perhaps less vigorous than those of the exogenous purins. Definite data upon this point have not yet been obtained.

### General and Nuclein Metabolism in the Gouty.

Progress in our knowledge of the pathology of gout has been hindered by the many factors which obscure a proper conception of the condition. The older observers had to work without the present-day knowledge of the chemistry of the nuclein bodies, and even during the dawn of the chemical era the methods available yielded but doubtful results. If, therefore, many honoured names and their associated observations escape mention, if some of the later works, in which the variety and quantity of food and the early or advanced stage of renal complications were not given due consideration, are omitted, it must be understood that it is not for want of grateful recognition of the valuable work carried out by the pioneers in this difficult field of inquiry. Many of them, mentally far ahead of the technique of their time, furnished suggestions and speculations upon which modern work has, to a large extent, been based, and the reader will find much food for thought, gain a deeper interest in this fascinating subject, and obtain suggestions as to future developments, if he will peruse some of the earlier books

written by those who, less pressed by the demands of modern life, had time to think placidly and to write sparsely.

In any discussion of the pathology of gout, it must be recognized that the condition is chronic in its course, and that, as a rule, during the early stages the patient does not show signs of any organic changes in the kidneys or liver. It is important, therefore, to select for investigation cases which are free from secondary or complicating factors. Similarly, the differences in the endogenous and exogenous metabolism must receive due consideration. Should it be necessary to refer to those inquiries which were planned and made prior to the period when the importance of the quantity and calorific values of the food taken was appreciated, and the effect of purin-free and purin-rich dietaries was estimated, the results must be used only after due allowance is made for the probable influence of these factors.

**The Energy Exchange.**—It is often said that the gouty patient has a "retarded metabolism." The statement is based upon the hypothesis that the excess of uric acid in gouty tissues arises from an insufficient oxidation of uric acid to urea. The supposed insufficient oxidation does not exist. Magnus-Levy found that the consumption of oxygen in seven gouty patients ranged from 2·41 to 4·33 c.c. $O_2$ per kilogramme and minute. Those are practically normal figures, and illustrate only the law that the consumption of oxygen varies with the size, weight, and obesity, of the patient. At the moment, however, it is not possible to advance evidence against the view that local decreases in oxidation may occur, and that the deposition of urates in certain tissues may be due to deficient oxygen exchange. Further observations are required.

Were it necessary to bring forward any stronger evidence against the view of "retarded metabolism and insufficient oxidation," there are several facts well known to the student of physiology. The excrements of snakes and birds consist chiefly of uric acid; the snake has a low body temperature and a low rate of oxidation; the bird has a high body temperature, and a high rate of oxidation. Frogs, on the other hand, have a low oxidation, but excrete their waste products chiefly as urea.

**The Protein Exchange.**—Here again a general retardation of metabolism does not occur. A summary of observations made upon cases in which the condition of the urine, heart, arteries, blood-pressure, etc., excluded any renal changes shows that, independent of the dietary, an increased decomposition of protein and nitrogen during the acute attack with its febrile changes is succeeded by periods of retention and irregularities in the output during the attack-free interval. A comparison of the nitrogenous equilibrium with that of the phosphorus equilibrium suggests that, at least in certain cases, the deficient nitrogen excretion is due to the

temporary accumulation of the nitrogenous decomposition products of protein.

Von Noorden placed a patient with chronic gout (well-defined tophi, no attack for two months, no evident renal or other complications) upon a constant purin-free diet. At the end of this period—the temperature remaining quite normal—the nitrogenous equilibrium was determined. The daily diet contained 18 grammes of nitrogen, yielding 45 calories per kilogramme, and consisted of two eggs, 2½ litres of milk, 200 grammes of white bread, 120 grammes of butter, and one apple. The fæces contained 1·8 grammes of nitrogen, and there was a daily action. The following results show the considerable variations in the nitrogenous output which occurred:

| Day. | Food Intake (Nitrogen). | Total Nitrogen excreted. | Uric Acid. |
|---|---|---|---|
| | Grammes. | Grammes. | Gramme. |
| 1 | 18 | 16·1 | 0·52 |
| 2 | 18 | 16·9 | — |
| 3 | 18 | 18·3 | 0·56 |
| 4 | 18 | 20·1 | 0·77 |
| 5 | 18 | 20·9 | 0·78 |
| 6 | 18 | 17·9 | 0·59 |
| 7 | 18 | 17·8 | 0·51 |
| 8 | 18 | 15·9 | 0·48 |

The objection may be raised that the patients upon whom these and similar observations were made had interstitial nephritis, or other renal changes, for some gouty patients do not show the nitrogenous variation—at least, they do not exhibit such changes during the short periods covered by recorded investigations. Von Noorden sums up the situation in the following words: "It would, indeed, be very remarkable if all these numerous patients were, notwithstanding, suffering with a severe kidney disease without albuminuria or some other symptom indicating the condition to clinically experienced observers."

There is a certain amount of evidence, therefore, to show that the protein metabolism of the gouty patient is somewhat unstable, and indicates a hypersensitiveness to disturbing influences.

**Carbohydrate and Fat Exchange.**—Carbohydrate metabolism is not disturbed to any extent. Starch, glucose, cane-sugar, and levulose are all well tolerated. Although glycosuria occurs in the gouty, it is not frequent. When it does appear it is alimentary in type, and is often associated with intestinal derangements or with chronic alcoholism. The metabolism of fat is not abnormal.

In about 5 to 9 per cent. of diabetics gout may be expected. The association of the two conditions has not been explained. More instances have been observed in France than in England.

**Digestion—Absorption.**—Acute gouty attacks are often associated with gastric or intestinal disturbance. Gastralgia, flatulence, constipation, or diarrhœa, are mentioned as precursors or accompaniments of the paroxysm. Too much has been made of this. The acute attack is an acute febrile condition, and certain gastric changes are nearly always present in fever. Von Noorden relates the history of thirty patients who had regular typical attacks of gout for many years. In these, with very few exceptions, the acute attack developed without any sort of a dyspeptic precursor. Of course, many gouty individuals suffer from gastric disorders, but these appear to be the result of varied dietaries and treatments rather than a part of the disease.

When the acute attack is a severe one, the secretion of hydrochloric acid is diminished. In mild attacks, and during the interval, the hydrochloric acid excretion is normal. Deficient HCl secretion is not a characteristic of gout. When such a condition is present, it is a complication due to general inanition.

Intestinal putrefaction is generally increased during the acute attacks, and is within normal limits during the intervals. It bears some relation to the dietary, for when a protein-free is substituted for a meat diet the signs of intestinal decomposition rapidly disappear.

The absorption powers of the gouty patient are not materially altered. Some patients show an abnormally large loss of fat and nitrogen in the fæces, but on the whole the figures obtained do not indicate any marked change from the normal. The fæcal nitrogen is generally a little high, but how far this is due to excess of bacterial content or to increased intestinal secretion has yet to be determined.

**Nuclein Metabolism in the Gouty.**—There is very little information available concerning the purin formation or destruction in gouty organs. Researches at present incomplete suggest that the gouty liver and kidney do not possess the average uricolytic powers of normal organs. The formed purin bodies, or cleavage products of nuclein, pass into the lymph and blood-stream, and are carried in an unaltered condition to the glandular organs.

Sir Alfred Garrod was the first to demonstrate the presence of uric acid in the blood of the gouty, and this he did by acidifying the serum and placing a piece of thread in it, when he observed that crystals of uric acid were deposited on the thread. His observations allowed him to state that the uric acid in the blood is increased at the time when there is a decrease in the urinary uric acid output. The following figures may be compared with those given under the headings of Temporary Uricæmias (p. 709):

| Observer. | | Amount of Uric Acid. |
|---|---|---|
| | In C.C. | Milligrammmes. |
| Garrod .. .. | 1,000 | 25 |
| Garrod .. .. | 1,000 | 30 |
| Garrod .. .. | 1,000 | 50 |
| Garrod .. .. | 1,000 | 110 |
| Garrod .. .. | 1,000 | 175 |
| Klemperer .. .. | 1,000 | 44 |
| Klemperer .. .. | 1,000 | 67 |
| Klemperer .. .. | 1,000 | 88 |
| Klemperer .. .. | 1,000 | 91 |
| Magnus-Levy .. .. | 1,000 | 30–80 |

Magnus-Levy did not find any valid variations preceding and during the acute attack in thirty-four estimations conducted with material obtained from seventeen patients.

These figures, however, do not afford any clue as to the source of the uric acid—that is to say, they do not indicate whether the uric acid found was associated with an intake of purin-rich or purin-free food. Brugsch and Schittenhelm have recently examined the blood of a gouty patient who for a long time had been kept on a purin-free dietary. The kidneys of the patient gave no clinical signs of inadequacy, and the heart and blood-vessels were normal. Uric acid was found to be present in the blood. Bloch, from determinations in a similar case, gives the following figures :

| Dietary. | Blood Quantity. | Amount of Uric Acid. |
|---|---|---|
| | C.C. | Milligrammes. |
| Purin-rich .. .. .. | 1,000 | 48·5 |
| Purin-free for two months.. | 1,000 | 44·5 |

Apart, therefore, from the metabolism of ingested purin material, it seems that in the gouty individual the endogenous uric acid carried in the blood-stream is present in excess, or in such a form that it is extracted easily during the ordinary methods of analysis.

**The Excretion of Purin Bodies in the Gouty**—*The Excretion of Endogenous Uric Acid.*—The gouty paroxysm is characterized by an increased output of uric acid in the urine. During the attack-free intervals the patient may excrete normal quantities of purin material, or quantities which lie at the lower physiological limit, or may show occasional increases or decreases. Gout

and nephritis are associated so frequently that it is important to know the average values for the urinary endogenous purins in normal and nephritic individuals. This is shown in the following table :

| | Endogenous Uric Acid. | Total Urinary Purin Bodies. | Urinary Purin Bases. |
|---|---|---|---|
| | Gramme. | Gramme. | Gramme. |
| Healthy person .. .. .. | — | 0·36–0·60 | — |
| Ditto .. .. .. .. | — | 0·35–0·63 | — |
| Ditto .. .. .. .. | 0·46 | — | 0·046 |
| Ditto .. .. .. .. | 0·38 | — | 0·030 |
| Acute hæmorrhagic nephritis .. | 0·31 | — | — |
| Parenchymatous nephritis .. .. | 0·43 | — | — |
| Interstitial nephritis .. .. .. | 0·45 | — | — |
| Ditto .. .. .. .. | 0·28 | — | — |
| Ditto .. .. .. .. | 0·51 | — | — |
| Gout: Attack free from intervals; no renal change .. .. .. | 0·41 | — | — |
| Ditto .. .. .. .. | 0·34 | — | — |
| Ditto .. .. .. .. | 0·39 | — | — |
| Ditto .. .. .. .. | 0·23 | — | — |
| Ditto .. .. .. .. | 0·30 | — | — |
| Ditto .. .. .. .. | 0·26 | — | — |
| Ditto .. .. .. .. | 0·12 | — | — |
| Ditto .. .. .. .. | 0·06 | — | — |

These figures, representing the results of a large number of reliable investigations, show that the output in gout varies with the individual, but that the endogenous purin excretion of the larger proportion of gouty patients approaches the normal. The gouty patient is usually on the border line of physiological and pathological uric acid excretion. The "renal" patients, on the other hand, maintain an average normal output, and it is general knowledge that the granular kidney excretes uric acid with ease, although it deals less thoroughly with urea.

Single day outputs, or even average outputs, however, do not afford a basis for an adequate conception of the uric acid excretion in gout. It is necessary to know whether the output remains unaltered during the acute attack and during the intervals of the attack.

*Acute Attack.*—For a few days prior to the onset of the acute attack there is a distinct decrease in the quantity of uric acid excreted. This, however, is not always present. When the pain is at its height the output is increased, the total quantity considerably exceeding the amount of the decrease, and being greater than the amount eliminated in correspondingly severe febrile conditions of different origin. The following table gives the figures obtained by Brugsch in a case free from renal complications :

| Diet. | Condition. | Urinary Endogenous Uric Acid. |
|---|---|---|
| | | Gramme. |
| Purin-free | Acute attack | 0·708 |
| ,, | Four days' interval | 0·376 (average) |
| ,, | Acute attack | 0·618 (one day) |
| ,, | Later days of attack | 0·375 (eight days' average) |
| ,, | Slight attack | 0·585 (two days' average) |

The increase in the output is succeeded by a decrease which continues for some time. It appears during the height of the gouty swelling or immediately after its subsidence.

*The Attack-free Intervals.*—In those cases in which the diet is purin-free, and the renal and circulatory conditions of the patient appear normal, there are greater variations than occur in the healthy individual on a purin-free diet. This is evident from the appended table, containing the results of an investigation by von Noorden upon a case three months after the last attack and six weeks before the next attack. The determinations commenced on the fifth day of a purin-free constant diet.

| Day. | Total 24 Hours' Uric Acid. | Day. | Total 24 Hours' Uric Acid. |
|---|---|---|---|
| | Gramme. | | Gramme. |
| 5 | 0·521 | 9 | 0·487 |
| 6 | 0·328 | 10 | 0·561 |
| 7 | 0·361 | 11 | 0·472 |
| 8 | 0·298 | 12 | 0·444 |

The conclusion is that, while the uric acid excretion of the gouty patient during the interval of the attacks is normal, or on the border line of the subnormal, there occur periodically considerable deviations from the usual average. Umber, who recently investigated 137 gouty cases, finds that the elimination of uric acid on a purin-free diet grows less and less until an attack of gout is pending, when the elimination rapidly increases, to reach its height about the second day of the attack.

*The Uric Acid Excretion of the Gouty on a Purin-containing Diet.*—When food containing purin is added to the dietary of the gouty patient, either at the time of the attack or during the intervals, the appearance of 40 to 60 per cent. of the ingested purin, which occurs in the average healthy individual, does not take place at once, but is spread over several days. The amount and rapidity of the increase depends upon the stage of the disease.

In the earlier experiments thymus, pancreas, beef, etc., were used as the purin-containing foods. It is not an easy matter to

insure accuracy by these methods, because of the varying purin contents of the meats and the idiosyncrasies of the patient with regard to the absorption of these substances, so that many of the figures previously relied upon must be discarded. Pure nuclein, or sodium nucleinate, permits of more exact calculations. Using these substances as the index of purin intake, recent investigators have shown that the exogenous purin exchange in the gouty is slightly less than that which obtains in the healthy, and that the period of excretion is prolonged.

On these grounds the following summary is permissible (von Noorden):

1. There are spontaneous periods of sufficient and periods of deficient uric acid excretion in the gouty.

2. The excretion is retarded and diminished when the gouty paroxysm is established.

3. The reaction to the intake of smaller amounts of purin bodies may be good, while it may be poor towards larger amounts.

4. Long administration of a diet poor in purin bodies seems to increase the power of eliminating uric acid.

Another remarkable feature is the deposit of urates, a subject which merits detailed consideration.

**The Deposit of Urates in the Tissues of the Gouty (Tophi).**—These "gouty deposits" are sometimes slight, sometimes extensive. When the deposit is expressed from early tophi freshly opened, it is seen to consist of soft, creamy material, alkaline to litmus and lacmoid, and composed chiefly of sodium biurate. Two analyses made by Ebstein and Sprague yielded the following composition:

| | Grammes. | Grammes. |
|---|---|---|
| Uric acid .. .. .. .. | 59·70 | 61·27 |
| Organic matter .. .. .. | 27·88 | 26·45 |
| $Na_2O$ .. .. .. .. .. | 9·30 | 12·28 |
| $Ka_2O$ .. .. .. .. .. | 2·95 | — |
| CaO .. .. .. .. .. | 0·17 | — |
| $MgO.Fe.P_2O_5S$ .. .. .. | traces. | — |

During the early stages of the disease tophi are formed slowly; in some typical cases of gout they are not present visibly; in the advanced stages they become prominent. Occurring practically in all types of tissue, they appear most frequently in cartilage. In articular cartilage the uratic deposit occurs first in the central portion as scattered or isolated points, streaks, or patches of chalky material. The urates lie between the cells of the subepithelial tissue, the epithelium being intact. The superficial layer is next eroded, and the articular surface becomes roughened and irregular. The deposits increase in size slowly, extend more deeply into the cartilage, and send out branches into the synovial membrane, tendons, and adjacent healthy tissue. At first consisting of urates only, they later may contain phosphate and carbonate of lime

also. Around them there appear collections of leucocytes and small round and giant cells; these commence to absorb the infiltrating salts. The tophus may slowly increase in size without any reaction, or an acute or subacute inflammation may supervene. In the latter case the tophi become stationary for a time, or may disappear as the inflammation subsides. When the uratic deposit occurs in gouty tendons, the areas of erosion show a definite relation to the vessels of the part, while in bone the tophaceous area is generally surrounded by distinct hyperæmia and massive accumulations of small round and multinucleated cells (Chalmers Watson). Then follow peri-articular thickenings and outgrowths.

Attempts have been made to reproduce these tophi by experimental methods. Ebstein obtained deposits of urates in the articulations, tendon sheaths, liver, and muscles, of fowls by ligaturing the two ureters, and so damming back the outgoing stream of urates. In another set of experiments he injected repeated small doses of neutral potassium chromate into animals, and so injured the renal epithelium and inhibited the output of urates. These deposits presented some resemblance to the gouty deposits in man. Around the areas which contained the deposits there appeared a zone of small-celled infiltration. Within the area patches of necrosis occurred.

His and Freudweiler injected mono-sodium-urate ($C_5H_3N_4O_3Na$) into the joints, peritoneum, and subcutaneous tissues of several types of mammals, and found that an inflammatory zone was formed around the injected material, and that necrosis occurred at the site of the injected urates.

Van Loghem introduced crystals of uric acid under the skin of rabbits, and observed that the uric acid crystals gradually disappeared, and that their place was taken by typical crystals of sodium urate. The area of urates was invaded first by polynuclear cells; giant cells next appeared; a zone of connective cells surrounded the area; the crystals were removed, partly by phagocytosis, partly by solution in the tissue fluids, and a patch of fibrosis resulted. When hydrochloric acid or sodium bicarbonate was administered to rabbits, and uric acid was subsequently injected, he found that in the acid-fed rabbit the formation of urates from the uric acid crystals was retarded or prevented, while in the alkali-fed rabbit the uric acid crystals were replaced rapidly by urates. In dogs, when uric acid was injected, it vanished completely in the tissues; but if large doses of sodium bicarbonate (30 grammes daily) were simultaneously given, deposits of urates occurred at the site of injection. When lithia, piperazine, citarin, lysidin, colchicine, sodium salicylate, citric acid, or solurol, were fed to the animals experimented upon, the injected uric acid crystals were unaffected. Silbergleit obtained similar results with uratic deposits in birds.

A summary of these experiments indicates than an increase of sodium chloride in the tissues means more rapid solution of uric acid, while an increase in the sodium carbonate content results in the formation of almost insoluble urates. Since we are at present ignorant of the conditions and combinations which are associated with the transport of uric acid in the tissue fluids, it is impossible to apply these results to human gout. At the same time it is probable that the varying sodium contents of the tissues may play a part in the formation of tophi. In this connection it is interesting to note that the tissues which are the more frequent and extensive seats of the uratic deposits are those which contain the largest percentage of chlorides. This is evident from the following figures:

| | NaCl per Cent. |
|---|---|
| Cartilage .. .. .. .. | 0·90 |
| Fibrous tissue .. .. .. | 0·70 |
| Synovia .. .. .. .. | 0·80 |
| Muscle .. .. .. .. | 0·08 |
| Liver .. .. .. .. | 0·02 |

Almagia injected uric acid into the peritoneal cavity of rabbits. After some days the joint cartilage gave a positive murexide reaction, while other tissues yielded negative results. He suggests that cartilage possesses high chemical and physical affinities for uric acid.

Kionka and Frey claim that when cartilage is bruised or damaged a considerable amount of glycocoll is formed. In normal cartilage glycocoll cannot be demonstrated. The addition of glycocoll to a solution of (neutral) di-akali-urate hastens the appearance of the (acid) mono-alkali-urate. When blood rich in uric acid circulates through damaged cartilage, the presence of the glycocoll may favour a precipitation of the urates. These facts and their deductions await further investigation, as the methods employed for the determinations were not entirely free from fallacies.

### The Metabolism of Salts, etc., in the Gouty.

*Ammonium Output.*—The quantity of ammonia in the urine of the gouty has a special interest, because the extent of ammonia excretion is regarded as an index of acidity, and because the chemical reaction of the blood has a special interest in connection with certain views upon the causation of gout. The result of a large number of estimations shows that the values for the absolute quantity of the ammonia excretion and its relation to the total nitrogen are within the normal limits.

*Mono-Amino-Acids.*—The average output for a healthy man varies from 1·3 to 2·8 grammes per day. The gouty patient does not exceed these quantities.

*Hippuric Acid.*—This also is not abnormal in the gouty (0·1 to 0·19 gramme per day under suitable dietary restrictions).

*Urobilin* is increased during the acute attack only. It is unaltered during the attack-free intervals.

*Phosphates.*—The excretion of organic phosphorus lies within normal limits. The relation of the earthy phosphates to the alkali phosphates is slightly changed. The normal quotient is 1 : 2·5. In some cases of gout this is extended to 1·4 or 1·5. The significance is unknown.

*Oxalates.*—Garrod found oxalic acid in the blood of gouty patients. Because of this fact, and because uric acid under the influence of oxidizing agents in alkaline solutions may yield allantoin, and ultimately oxalic acid and urea, Garrod's observation possesses great interest. Only one exact investigation is available. Mohr and Salomon found in the urine of a chronic gouty patient on a mixed hospital diet 4·4 to 7·1 milligrammes of oxalic acid per day. These figures lie at the lower limits in healthy subjects under similar conditions.

*Chlorides.*—There is a delay in the excretion of chlorides when renal complications ensue. What happens during the other stages is not known. Normal individuals vary considerably in their power of excreting sodium chloride, the variation being as much as 31 per cent. from the average. It is probable that the tissue content of chlorides may play an important part in connection with gouty deposits. Further information is desirable.

### The Stages of Gout in Relation to Morbid Changes.

In view of the numerous hypotheses which have been put forward to account for the cause of the gouty process, the lesions associated with the condition demand consideration.

Perhaps the most striking fact is what may be termed " the variations in the intensity of the goutiness." In one case a gouty patient may pass through his existence with but one—or without even one —acute attack. In another the attack may be annual or monthly. Here alimentary conditions, there renal conditions, are the feature. The location, the intensity, and the rapidity, of the process are rarely similar.

The arthritic conditions are one of the chief and earlier features ; the kidneys at first are generally fairly healthy, and the heart and blood-pressure are not more than the patient's age would account for. Endogenous uricæmia, however, is a definite entity, although the output of uric acid is only slightly subnormal,and the metabolism of food nucleins is but slightly delayed. This is the stage that has been taken for the basis of the figures already quoted, and which offers the best field for the discovery of the causal factors.

It is possible to recognize (1) a purely metabolic form of gout, (2) a renal form of gout, and (3) a combination of the metabolic and renal forms.

Under the metabolic forms of gout albuminuria may occur. This is probably connected with the febrile disturbances. At any rate, it does not usually lead to acute nephritis. Repeated attacks of a similar kind may result in degenerative changes of a permanent kind, and this is the explanation often given of the association of long-standing gout with chronic interstitial nephritis. Some persons, however, have gout all their lives, and yet the kidneys are found healthy in post-mortem examinations, or show atheromatous changes only.

The "gouty kidney" is often red, atrophic, with granular surface and adherent capsule. The interstitial tissue is increased and fibrous. The glomeruli are scanty, atrophic, hyaline, fibrous, or cystic. The secreting tubules are less affected than in pure chronic interstitial nephritis. The lesions are localized, not diffuse. The vessels are sclerotic, and the change in the tubules may be a result of imperfect circulation. The chief features are (1) deposits of urates in all parts of the parenchyma, interstitial tissue, and pelvis; (2) the senile changes, gout being more manifest in the later half of life, lasting many years, and being rarely fatal of itself. But as a rule there is more interstitial change than can be ascribed legitimately to senility alone, and these morbid changes show that, at all events during the later years of life, the condition of the kidney affects the urinary output. In the other types of chronic interstitial nephritis, however, the uric acid excretion is rarely much diminished, and the uratic deposits due to retention are only slight, so that the amount of functional tissue present in the contracted kidney of chronic interstitial nephritis suffices, apparently, to eliminate an average output of uric acid. The clinical course of this condition is different also from that of gout. Chronic interstitial nephritis terminates life in the early twenties or fifties. Gout is a more chronic condition, and in itself is rarely fatal. While, therefore, gout may cause a slowly progressive degeneration of the cells of the renal tubules and interstitial fibrosis, and may accelerate senile, vascular, and parenchymatous changes, it does not cause the typical disease known as "chronic interstitial nephritis," and the nomenclature ought to be adjusted accordingly. At the same time it is possible that gout and chronic interstitial nephritis may be accidentally associated without there being any causal connection between the two. It has to be borne in mind, also, that in some cases of gout the renal changes occur earlier than in others, and that in such instances retention of purin bodies may occur. In addition, a patient who is the subject of chronic interstitial nephritis may thus be predisposed to gout. There is no basis yet for assuming that the cause of gout produces also the renal changes; on the other hand, it appears probable that it is the results of the gouty process which are responsible chiefly for the kidney alterations.

Gout is said to be one of the causes of atheroma. There is a doubt about this. Atheroma has been produced experimentally

by increasing the blood-pressure and by the administration of certain toxic substances. It is a very general condition in old people. At the most, it is considered by some that gout only intensifies or aggravates the natural tendencies of age.

Abelous states that in normal urine two bases are present which produce a rise of blood-pressure. Bain found that these bases were decreased in gouty urine. The suggestion is that they are retained, and are the cause of the increased blood-pressure. If these results are confirmed, a new field of work will be opened up.

The early stages of gout are associated with certain cardiac functional changes. Tachycardia, bradycardia, syncope, angina pectoris or anginoid attacks, may alternate with pure gouty paroxysms or follow digestive disturbances. Later, definite organic changes may ensue in untreated cases, and sclerosis of the coronary and systemic arteries appears; the aortic valves may be affected similarly. Phlebitis is a common condition in the gouty. It is, however, frequent apart from gout, and may be regarded as secondary rather than primary.

In the stomach and intestines there are no definite organic changes in the mucosa, transitory alterations in the digestive functions leaving no specific effect upon the tissues. The flora is not altered appreciably, and observations extending over a number of years have not revealed any abnormally predominant organism. The liver in the later stages is fatty and cirrhotic; these changes correspond in extent to the amount of the arterio-sclerosis.

The changes in the nervous system are chiefly those due to vascular degenerations. They occur later than similar conditions associated with chronic interstitial nephritis, but earlier than the average period of senile changes. Accordingly, they may be classed under the heading of "premature senility." They consist of articulatory difficulties, loss of memory, diminished power of concentration, and a tendency to emotional instability. Neuritis is a common lesion: sometimes it is associated with the arthritic changes; sometimes it is quite isolated. Uratic deposits occur in the nerve sheaths, and areas of glossy skin and atrophic muscles indicate the extent of the trophic changes.

In addition to the joint lesions already described, localized erosions of bone have been observed in the phalanges. They are situated near the diseased joints, but do not communicate with them. They contain deposits of urates and a gelatinous substance of undetermined composition. In the bone marrow uratic deposits also occur, and these may be intersected by trabeculæ of dead bone. Suppuration is not a feature unless a secondary infection ensues.

### Lead Gout.

A connection between lead-poisoning and gout has long been known. Alfred Garrod, in 100 cases of gout, found 33 cases of lead-poisoning, and Dyce Duckworth observed 25 out of 136.

It is curious, however, that the incidence varies in different localities. In the Newcastle district, Oliver states, gout is rare in native lead-workers, although workmen who come from the South develop the disease. In Berlin, Frerichs did not find a single case of gout in 163 cases of lead-poisoning.

Experimentally, lead causes at first degeneration of the renal cells, and later interstitial changes in addition. In many cases of lead-poisoning the kidneys are found to be granular when examined post mortem.

Clinically the gouty lead-worker presents the typical tophi and other signs, but there is generally a definite anæmia and cachexia also. The duration of the disease is shorter than in ordinary gout. The blood contains an excess of uric acid, and the urinary purin output follows a similar course to that of "metabolic" gout.

It is possible that lead, being a general protoplasmic poison, may modify the general metabolism of the body, and so affect the formation, transport and elimination of purin material that uricæmia and uratic deposits result.

## Etiology.

*Age.*—Gout does not commonly appear under the age of thirty-five, but it may occur earlier in members of families in which there is a marked hereditary tendency.

*Sex.*—Gout is more common among males. It rarely attacks women; when it does, its intensity is generally increased. Hippocrates makes the following statements, to which further reference will be made: "Eunuchs are neither troubled with gout nor baldness." "A boy is not troubled with gout till he has used venery" ("Aphorisms," vi. 28, 30).

*Heredity.*—The male children of gouty patients are prone to develop gout if they live under conditions suitable for the development of the disease. The female children frequently escape gouty attacks, but transmit to their children the disease or the tendency thereto; they may, however, themselves be the subjects of "irregular" gout. The following table by Luff is instructive:

| | Per Cent. |
|---|---|
| From one or both parents only .. .. .. .. .. | 24·6 |
| From one or both grandparents only .. .. .. .. | 17·6 |
| From one or more grandparents and one or both parents .. | 16·8 |
| From one or both parents and other members of family (not grandparents) .. .. .. .. .. .. .. | 15·6 |
| From one or more grandparents and other members of family (not parents) .. .. .. .. .. .. | 9·4 |
| From one or more grandparents, from one or both parents, and other members of family.. .. .. .. .. | 9·0 |
| From members of family not grandparents or parents .. | 7·0 |

This table shows that in 27 per cent. of the cases the disease was

transmitted from grandparents to grandchildren without the fathers or mothers suffering from active gout.

Of the cases inherited from the parents only, the following is the distribution of the heritage :

| | Per Cent. |
|---|---|
| From the father only | 73·4 |
| From the mother only | 11·6 |
| From both parents | 15·0 |

Of the cases inherited from the grandparents only, the following is the distribution of the heritage :

| | Per Cent. |
|---|---|
| Paternal side | 53·5 |
| Maternal side | 21·0 |
| Both sides | 25·5 |

*Habits.*—Excessive intake of alcohol and nitrogenous food are often met with in the gouty. On the other hand, deficient food with insanitary surroundings and excess of malt liquors are also associated with attacks of gout. Sedentary occupations and inadequate physical exercise constitute another set of factors.

*Influence of Other Diseases.*—Lead-poisoning predisposes to gout. Acute febrile diseases, such as tonsillitis, bronchitis, rheumatism, etc., afford relief from the constitutional symptoms, and appear to render the patient free from paroxysms for some time.

*Primary Cause.*—Acute attacks are often attributed to unusual indulgence in food or drink, or some unusual mental emotion such as might be induced by a fit of anger, worry, or anxiety. Exposure to cold or injury are also cited as possible excitants. It is probable, however, that many of these may be due to the onset of the attack. The actual cause of the acute as well as of the chronic condition is not known.

## Summary of the Chief Factors in Gout.

The features of gout which are sufficiently well established to call for an attempt to explain their etiology may be summarized as follows :

1. Acute attacks of pain, located in joints, organs, or tissues, accompanied by fever. They are liable to recur and produce permanent tissue changes and deformities.
2. Uricæmia of endogenous origin, with a urinary purin output approaching the lower physiological limits ; one portion of the purin material may be extracted from the blood easily, the other with difficulty.
3. Uricæmia of exogenous origin, with delayed but not markedly decreased urinary purin output.
4. Defective uricolysis.
5. Slow continuous decomposition of urates in all tissues. These

are most evident in tissues with retarded circulation. Under certain conditions these deposits may partially or entirely disappear.

6. Periods of retention of nitrogen and periods of increased nitrogenous elimination.

7. Increased nitrogen and purin output during the febrile periods.

8. Numerous functional changes.

9. Tendency to earlier onset of senile changes, particularly vascular degenerations and interstitial fibroses in kidney, liver, and heart.

The most evident factor in gout is the permanent uricæmia and uratosis. This permanence is in marked contrast to the temporary uricæmias. The idea that uric acid plays any part in the etiology of the disease must be definitely discarded. The uric acid prominence is a result of some unknown cause, and merits consideration only so far as a study of its extent and associations opens the way to a clearer conception of the actual etiology of the gouty conditions. How and why does it arise ? From time to time it has been ascribed to (1) increased formation ; (2) deficient destruction ; (3) deficient destruction plus renal retention ; (4) defective or abnormal combinations during transport ; (5) an inborn defective metabolism of nuclein.

*Increased Formation.*—At the present stage of our knowledge this may be disregarded. The gouty patient is usually put upon a purin-poor dietary. There is no leucocytosis ; no signs of an increased nuclein decomposition except a few records of slightly increased phosphoric acid excretion, and these are difficult of interpretation ; there is rarely any excessive muscular exercise leading to the formation of hypoxanthin and its oxidation to uric acid ; the functional metabolic changes are not maintained at a supernormal level, and the uric acid output is low except during the febrile periods.

*Deficient Destruction.*—Published and unpublished observations suggest that, when compared with normal organs, both the liver and kidneys of gouty individuals exhibit a slowed and diminished breaking down of uric acid. Such determinations, however, are rarely possible except with organs obtained from cases so far advanced that cirrhotic changes are present. It is a little difficult to apply them to early and uncomplicated gout. Uricolysis is most marked in the kidney, and if the uricæmia is due to a defect in this process an increased output of unaltered urinary uric acid,as well as an increased amount of uric acid in the blood, might be expected. This is not so. The excretion of uric acid is normal or subnormal.

It has been claimed that deficient and slow fermentation processes obtain in gout. Further evidence may soon be brought forward to support this attractive hypothesis.

*Defective Elimination.*—The possibility that the uricæmia is due to a deficient excretion of uric acid by the kidney has long been held. Earlier determinations of the uric acid output in nephritis sup-

ported this view, but by the use of better methods it is now evident that renal changes do not seriously alter the uric acid content of the urine. In addition, the gouty patient excretes exogenous purins well, though slowly. During the first years of gout marked morphological changes do not appear in the kidney, and it is with this type of case that investigations should be continued. When a number of doubtful points in connection with this stage have been cleared up, it will be time enough to turn attention to more advanced stages. Even in the last months of nephritis, there is a more prompt reaction to the addition of purin substances than occurs in the gouty. The balance of opinion is against the view that defective elimination is due to interstitial changes in the gouty kidney.

We cannot, however, exclude the possibility that with the onset of gout the renal cells may be influenced by some abnormal substances, so that they are unable to remove uric acid from the blood except when the solution tension reaches a higher limit than is the case in nephritis (Magnus-Levy and Minkowski).

*Defective or Abnormal Combinations during Transport.*—It is a significant fact, already mentioned, that when an animal is fed with excess of nuclein-rich food uric acid appears in the blood in at least two different combinations. One portion may be separated by the centrifuge; the other requires a method of extraction before it can be isolated.

Pfeiffer first laid stress upon this point, basing his views upon a diminished alkalinity of the blood-stream. Recent work has shown that this diminished alkalinity does not exist; in fact, during the acute attack the alkalinity may be increased.

Minkowski made the suggestion that under normal conditions uric acid circulates in combination with some of the cleavage products of nucleic acid, such as thymic or nucleotin-phosphoric acid. The evidence brought forward is not very convincing.

In spite of this lack of evidence, it is exceedingly probable that uric acid does circulate in some form of organic combination, and that this compound is less stable, or absent, in gout, so that fermentative tissue changes, such as uricolysis, etc., are hindered. Further work is necessary for the clearing up of some of these difficult problems. For instance, when formaldehyde is added to uric acid a uric acid compound results which is protected from further oxidation, and inverse conditions might well obtain with other compounds. Von Noorden goes so far as to say that "to become master of this question is one of the most important problems in the investigations of gout."

*Inborn Defective Metabolism of Nuclein.*—A number of conditions are already known in which the intermediate cell metabolism is at fault. Diabetes, obesity, alcaptonuria, pentosuria, and cystinuria, come under this heading. In pentosuria, arabinose appears in the urine as a result of cell metabolism, its output is not influenced by diet,

and when arabinose is added to the dietary the exogenous pentose is utilized, and does not increase the amount of the endogenous portion. Similarly, cystin is excreted by the cystinuric, and is not affected in proportion by dietetic changes. In a case reported by Abderhalden all the organs contained deposits of cystin crystals, and he was able to separate pure cystin from the spleen. This is an example of an altered intermediary metabolism of protein material, the cystin—at least in many cases—being derived from protein. It does not seem impossible that an analogous condition may obtain in connection with the metabolism of nuclein, and form an explanation of the gouty uricæmia. Little is yet known concerning the circulation and output of the purin bases in gout. The investigations which are now being directed to the point may yield the necessary evidence.

### Hypotheses as to the Cause of Gout.

So many views have been advanced with regard to the etiology of gout that it is a difficult matter to present them in orderly fashion. Few have stood the test of time; few have sufficed to explain more than a partial aspect of the disease. When it is conceded that the manifestations of the condition are not confined to the uricæmia and the uratic deposits, but that gout is a general disease, chronic in type and metabolic in character, it will be understood that a better knowledge of its cause must wait upon the developments of chemistry and physics, and that our ideas may change as these sciences progress towards their respective goals.

It is of interest and value, therefore, to review briefly the various hypotheses which in their time have been considered as the best explanation of the disease, in order at length to command the outlook which now confronts those who are endeavouring to get nearer to the hidden primary cause.

The hypotheses already advanced may be considered under the following headings:

1. Those supposing uric acid or other purins to be the initial cause: (*a*) the uric acid or its compounds may act as a mechanical irritant; (*b*) the uric acid or its compounds may act as a chemical irritant; (*c*) the purin bases may act as irritants.

2. Those supposing that gout arises from nerve lesions.

3. Those supposing that gout is an intoxication: (*a*) the toxin may be autotoxic; (*b*) the toxin may be bacterial in origin.

4 Those supposing that gout is due to a defect in the intermediary metabolism: (*a*) the defect may lie in altered carbohydrate fermentation; (*b*) the defect may lie in altered nuclein fermentation; (*c*) the defect may lie in altered processes other than fermentative.

5. Those supposing that gout is due to some general disturbance of which the defective nuclein or purin metabolism is only one factor, other symptoms being connected with cardiovascular, nervous, and tissue lesions in which urate deposition plays little or no part.

1. **Uric Acid or Other Purins the Cause of Gout.**—Uric acid is a dibasic acid which has two atoms of replaceable hydrogen. It is also a diureid; that is, its molecule contains two urea radicals joined together by a tricarbon group. It never occurs in the free state in the blood or tissues, either under physiological or pathological conditions. It forms two groups of salts, and occurs in the body as a compound. When sodium is taken as the replacing metal, the following substances are said to result:

(1) Neutral sodium urate—$Na_2C_5H_2N_4O_3$.
(2) Acid sodium urate—$NaHC_5H_2N_4O_3$.
(3) Quadriurate—$NaHC_5H_2N_4O_3$–$H_2C_5H_2N_4O_3$ (Roberts).

The neutral sodium urates are unstable compounds, and are not present in the human economy. The biurates are met with in tophaceous deposits; they are not believed to occur physiologically. Sir William Roberts supposed that uric acid appeared in the blood-stream in the form of a quadriurate. It is doubtful if this compound is ever formed.

(*a*) *Uric Acid acts Mechanically in its Crystalline Condition.*—Sir Alfred Garrod held that the acute gouty attack was due to the deposition of sodium biurate in tissues predisposed for its reception. The predisposition arose from former injury or disease. When deposited, the crystallization of the biurate evoked the inflammatory changes.

Sir William Roberts and Cornil and Ranvier supposed that the crystalline uratic deposit itself, acting mechanically as a foreign body, was sufficient to cause the pain, swelling, and reactive changes, of the acute attack, as well as the manifestations of irregular gout in liver, heart, or nervous tissues. Sir William Roberts thought also that scattered needles of sodium biurate in the blood might form foci around which coagulation would occur. In this way he explained the thromboses which are sometimes met with in gouty cases.

When these views were enunciated the following criticism was evoked: "If the crystalline sodium biurate acts as an irritant, how is it that the semisolid urinary excrement of birds and serpents, which is composed of uric acid with a small percentage of purin bases, does not irritate the kidneys during excretion?" The reply to this was that this excrement is composed of an amorphous urate which is non-irritant, and that it is possible that the urates pass through the kidney tubules in gelatinous form, and so the mechanical irritation is avoided.

Again, if the crystalline deposit provoked the acute attack, it

seems probable that a continuous irritation and inflammation would be kept up until the sodium biurate was removed. The total disappearance of the biurate is rare; continuous deposition is the more frequent course. But the inflammation subsides after a few days, and the tophus becomes enlarged. This is against the view that the urates cause the condition; it rather suggests that the inflammation precedes the biurate deposit, and that the latter, in some way or another, is a corollary to the inflammatory process.

(*b*) *The Uric Acid or its Compounds act while in Solution as a Chemical Irritant.*—Pfeiffer suggested that in gout sodium biurate was deposited in healthy and diseased tissues without producing any marked symptoms, but that, owing to some increase in the alkalinity of the blood, the deposited urates were redissolved. These dissolved urates passed into the general circulation, the general tissues were flooded with a chemical poison, and an acute attack resulted. It is known now that increased alkalinity diminishes the solubility of sodium biurate, so this view has become untenable.

Ebstein advanced the hypothesis that uric acid or one of its compounds—neutral sodium urate in particular—produces necrosis in cartilage and similar tissues, and that biurates are deposited in the damaged structures. He described the gouty process as commencing with a stasis of the lymph stream in the affected area, and a subsequent infiltration with neutral urates; the latter cause necrosis of tissues; during the necrosis a free acid is liberated; these changes irritate the adjacent areas, and the inflammatory acute attack is produced. He supported his views by some experiments upon birds, in which, by ligaturing the ureters or damaging the kidneys by injection of neutral potassium chromate, he found that uratic deposits occurred in the tissues, and that in these areas necrosis and inflammatory reaction followed. The result is quite what would be expected. A natural excretion is stopped suddenly, and it accumulates in the tissues—a process in no sense comparable with gout. Ebstein, however, did not rely on these experiments alone. He added uric acid to a 5 per cent. solution of sodium phosphate, and injected it into the peritoneal cavity, into the anterior chamber of the eye, into the cornea, and into the cartilage of the ears, of a rabbit. Powdered uric acid was also placed in the conjunctival field of one eye. In the cornea there was considerable reaction, and Ebstein concluded from this and other reactions he was able to induce that uric acid acted as irritant.

These views have not gained wide acceptance, for the following reasons: (1) Uric acid (*a*) is not a toxic substance. It may be given to animals in large doses with their food, or injected into their veins, without causing any signs of poisoning. (*b*) It has no effect upon nerve-muscle preparations. (*c*) It may be given to patients suffering from chronic nephritis in quantities as large as 3 grammes daily without causing any systemic disturbance. (*d*) In leukæmia

it occurs in the blood in large quantities without causing any ill effects. (2) The neutral sodium urate is decomposed in the presence of carbonates, so that it cannot exist in the blood, and it is extremely unstable.

(*c*) *The Purin Bases are the Causes of Gout.*—Kolisch suggested that the purin bases were the cause of gout. He stated that gouty urines contained an excess of purin bases. At the time it had just been demonstrated that the amino-purins acted deleteriously upon the renal cells, and, when injected into animals, produced deposits in the renal tissues. Subsequent extended investigations showed, however, that the purin bases were not excreted largely in gouty urine, and the hypothesis became untenable.

2. **Gout is due to Nerve Lesions.**—In this hypothesis the essential cause of gout is attributed to a functional disturbance of an area in the medulla oblongata. As a result of this disorder a defective metabolism arises which is responsible for an undue formation of uric acid and a diminished destruction. The acute attack is thought to arise from the instability and undue sensitiveness of the nervous system, or from a direct stimulation of the sensory nerves by uric acid. The joint deposits and tophi are secondary to the nutritive or inflammatory changes. In primary or inherited gout the condition is dependent upon the inherited gouty neurosis. In secondary or acquired gout alimentary or excretory overloading leads to a toxæmia which induces depression and exhaustion of the nervous system, and the gouty neurosis becomes established.

These views have of late been pushed in the background, but it is probable that in a modified form they may again have their day.

3. **Gout is an Intoxication**—(*a*) *The Toxin is Autogenous in Origin.*—When it was established that uric acid did not possess any toxic properties, it was tempting to assume that a toxin of some kind or other was responsible for the causation of the gouty changes. The association of the acute attacks with mental and intestinal aberrations suggested that in connection with the metabolic processes a substance was evolved which on the one hand produced the symptoms of the acute attack, and on the other hand maintained the chronic manifestations. By some the unknown toxin was supposed to act generally, by others locally. In the former case it was responsible for the uricæmia which led to the deposition of urates from an over-saturated solution, and secondary pressure atrophy resulted; in the latter it produced, at the points of least vitality, death of cells and subsequent breaking down of their nucleins to form urates and uratic deposits.

Although this hypothesis may contain much of the real truth, its very indefiniteness seems to have been responsible for the development of the idea that—

(*b*) *The Toxin is Bacterial in Origin.*—The exponents of this view based their hypothesis upon the likeness of the acute gouty joint

to the joint changes occurring in rheumatism, septicæmia, scarlatina, and allied diseases. The chronic gouty lesions of the skin, respiratory, circulatory, and renal tissues, form also a group which have marked toxic analogies, and can be best explained by a toxin circulating in the blood-stream.

The source of this toxin is probably the alimentary canal. Owing to some catarrhal or inflamed conditions, the natural antibacterial secretions are lessened, the growth of the normal flora is not so well controlled, and the increased excretions or toxins pass through the weakly resisting mucosa into the portal circulation; or it may be that some bacteria, under altered surroundings, assume distinct pathogenic characters. If these toxins reach the tissues of healthy people they are neutralized rapidly, and no ill effects result; but when the toxins pass the normal detoxicating barriers, such as the liver, etc., and gain the general circulation, the tissue cells are unable to resist the toxic action, and cellular and nuclear reaction or degeneration follows. This liberates a large amount of nucleinic derivatives, and an excess of uric acid formation is occasioned.

The tendency to this intestinal catarrh may be inherited, and it is possible that the flora of the gouty may show variations from the normal. So far this has not been demonstrated, and no organism specific for gout has been discovered.

Trautner holds that a mucous colitis is one of the first manifestations of gout, and that the *Bacillus coli communis* is the primary cause. He considers that the *B. coli* produces a reducing substance which is transformed into xanthin and uric acid during its passage through the body. Others point to the prevalence of pyorrhœa alveolaris, and the possibility of the introduction of virulent streptococci, etc., via the intestine.

The action of purgatives in removing the intestinal contents, and thus limiting the acute attack, is also cited as an evidence of the toxicity of the flora of the intestine; purgation, however, is a measure which is employed with success in many febrile conditions due to extra-alimentary causes.

If a specific micro-organism is the cause of gout, its isolation is simply a matter of time. The indictment of the entire normal intestinal organisms suggests that the hypothesis is rather concerned with the lowering of the bacteriolytic or toxin-destroying properties of the liver, and that the theory is bacterio-hepatic rather than purely bacterial.

4. **Gout is due to a Defect in the Intermediary Metabolism**—(*a*) *Defective Carbohydrate Fermentation.*—Hare has pointed out that while the human body deals rapidly and extensively with large quantities of nitrogenous material, its power for the catabolism of carbonaceous compounds is strictly limited. Hence there is a marked tendency for the accumulation of carbon contents in the blood-stream. This excess of carbonaceous material is commonly

present in such paroxysmal conditions as asthma, epilepsy, and migraine, and instances have occurred in which an attack of gout has coincided with the subsidence of long-standing migraine or epilepsy, and *vice versa*.

The hypothesis is therefore advanced that liberal supplies of carbohydrate food, coupled with deficient exercise and consequently diminished combustion, lead to a stage which, under certain conditions, may culminate in acute gout. The pyrexias of the acute attack act curatively in removing the excess of carbonaceous material. Irregular or suppressed gout is also attributed to the same cause.

This view explains a possible factor in the condition, but does not afford any indication as to the underlying cause of the uricæmia and vascular changes.

(*b*) *Defective Nuclein Fermentation.*—It has been found that certain surviving organs and tissues contain ferments which are able on the one hand to break down amino-purins, such as adenin and guanin, into mono- and di-oxypurins, xanthin, and hypoxanthin, or to form the tri-oxypurin, uric acid, from the di-oxypurins; and on the other hand to break down uric acid into urea and other bodies. There is every reason to suppose that these ferments act similarly during life, and to conceive that the metabolism of endogenous, and possibly of exogenous, purins is carried on in this manner. If such be the case, variations in the type or extent of the process may lead to disturbances of the intermediary metabolism.

So far it has not been shown that the purin bases are in excess either in the blood or the urine. More investigations are required on this point.

At the moment attention may be confined, therefore, to the actions of ferments upon uric acid. A number of deviations from the normal are possible:

1. The ferments which transform uric acid into the compound in which it usually circulates may be normal in amount, but the amount of uric acid may be in excess. This results in an excess of uric acid in the blood-stream, as in pneumonia, leukæmia, and during an excessive intake of nuclein.

2. The ferments may be able to transform the uric acid properly, but the renal cells are unable to remove the uric acid from the blood, except when the acid reaches a definite higher concentration. This might occur in nephritis or when there is a specific gouty renal inadequacy.

3. The ferments may be defective in quantity or type, and are thus unable to transform the uric acid into an "excretable" compound. This would be an anomaly of metabolism, which might be characteristic of gout.

These suppositions form a suitable starting-point for further work; but even were they entirely proved, they would in themselves

not account for the onset of gouty paroxysms. Nevertheless, further researches on these lines may reveal etiological factors for the acute attack also.

Comparative pathology yields some interesting facts in this connection. In pigs a condition of guanin gout has been described. Guanin appears in the urine, and tophi, composed chiefly of guanin, are formed in the joints and muscles. Normally, pig's urine contains uric acid and purin bases only, and deposits are not present in the tissues. This guanin gout of pigs might be explained by defective fermentative changes of one of the amino-purins.*

(c) *Defective Processes other than Fermentative.*—Kionka has shown that glycocoll, when added to a neutral solution of di-alkali-urate, hastens the appearance of the acid urate, while urea inhibits the formation of the acid salt. Normally, glycocoll is almost entirely transformed into urea in the liver; but if the urea ferment action of the liver is depressed, then more glycocoll passes into the blood-stream, and the uric acid will be thrown out of solution. When this obtains, glycocoll ought to be present in considerable quantities in the urine. This seemed to be the case at first, but extended investigations showed that the glycocoll excretion is inconstant both in normal and in gouty urines, and that an excess of glycocoll is not regularly excreted by the gouty patient. Similarly, it was at one time held that, when cartilage was bruised or damaged, a considerable amount of glycocoll was formed, and it was suggested that the presence of the glycocoll would explain the precipitation of urates in cartilaginous tissues. These contentions met with considerable criticism, and further inquiry showed that the results upon which these views were based were within the limits of experimental error.

Attempts were made also to show that glycocoll is formed in the tissues during uricolysis, just as it is when strong hydrochloric acid is allowed to act upon uric acid at a high temperature. The attempts failed.

Under certain conditions blood is able to transform uric acid into glycocoll and other substances. There seems little doubt, however, that the blood during circulation does not act otherwise than as a passive transporting agent.

Shearer suggests that an excessive quantity of $CO_2$ in the arterial blood is a condition which leads to gout, arterio-sclerosis, etc. Exercise has, consequently, a beneficial effect upon those subject to gout, because it increases the exhalation of $CO_2$ from the blood. But, as Hare points out, exercise increases not only the exhalation, but also the $CO_2$ production.

Falkenstein believes that a diminished secretion of hydrochloric

* Defective fermentation in the human subject is said to occur. Uric acid may be entirely absent from the urine, its place being taken by the several purin bases.

acid in the stomach leads to a diminished decomposition of nuclein, and to a deficient oxidation of uric acid to urea, etc. The system thus becomes overloaded with uric acid, and gout results. The administration of hydrochloric acid, he claims, facilitates the decomposition of uric acid, and lessens the output of uric acid in the urine. While it must be admitted that the introduction of chlorides into the tissues in this way may be good therapy, it must also be pointed out that there are numerous pathological conditions in which HCl may be absent from the stomach for a long time without any symptoms of gout arising. Further, it has been shown that numerous gouty patients secrete normal quantities of hydrochloric acid, and that the administration of hydrochloric acid in gout is generally accompanied by a slight rise in the uric acid output; rarely is it that any diminution appears.

5. **Gout is a General Disturbance, of which the Variations in the Purin Metabolism are only One Symptom.**—As many of the hypotheses advanced as an explanation of the gouty process stand practically abandoned, and many of those which still command adherents account but for one or other of the manifestations, there is a tendency among some pathologists to look behind the variations of purin metabolism and the action of tissue ferments on the waste products of nuclear activities, and to foreshadow a conception of the existence of a general disturbance of which the purin changes constitute one set of symptoms only. This has not yet been definitely enunciated as a hypothesis, and it must not be so regarded. It is rather a series of forecasts of possible lines of inquiry.

One of the striking facts brought out during the last few years is that in the gouty individual the metabolism of the exogenous food-purin moiety shows little deviation from the normal, except that it is slower. It has been shown also that it is possible to find out the exact quantity of purin containing food which can be dealt with—in other words, the "tolerance" of the patient for food purins may be ascertained. When this has been determined, it is recommended to raise the intake gradually, and in this way to raise the "tolerance." In spite of this, however, the gouty endogenous uricæmia persists. This suggests the question as to whether there is any molecular difference between the nuclein bodies in the food, derived as they generally are from healthy cells, and the nuclein cleavage products of the human gouty cells. If gout is due to the chronic action of a toxin, is this toxin so selective that it influences the fermentative processes connected with human-cell metabolism only, or alters the renal cells in such a manner that they select human purins with greater difficulty than animal purins? It does not at first sight seem so necessary that the food nuclein should undergo the transformation that the food albumin undergoes before it reaches the general circulation. Estimations of the nuclein contents of hen's eggs, and of the total tissues of fœtal and young suckling rabbits,

show that cell nuclein is formed by the growing animal from non-nuclein food.

Another fact which has of late been emphasized is the importance of the cell nucleus in the life-processes of the cell. Purin metabolism is concerned with that part which initiates and directs the processes of cell life. While there is general agreement that gout is associated with some fault in the nuclear part of the cell metabolism, the feeling gains ground that too much attention has been given to the end-products of nuclein metabolism. It is high time to examine more closely the nucleus itself, and endeavour to discover the "how and the why" of its activities. Perhaps it may be found that certain changes in the end-products originate in the individual characters of the nuclei.

In diabetes, obesity, and several other conditions, the cell nuclei of a large number of tissues exhibit inborn peculiarities with regard to the metabolism of sugar, fat, and protein, in that they are more or less unable to effect the assimilation and cleavage of these substances. The result of this is that some incomplete metabolites, useless for the general purposes of economy after circulation in the blood-stream, are excreted in the urine or deposited in suitable places. Is it possible that in gout a similar condition obtains? The nuclei may work defectively or display individual idiosyncrasies. Ferments insufficient or inappropriate are unable to overcome the initial error. For some time the excretory organs, working at unusual pressure, cope with the difficulties. After a time, owing to the overstrain, they become less effective, and the imperfect metabolites are partially retained and deposited in suitable areas. Whether this be true or not, it will be admitted that the cells of the gouty individual have to live in, and to absorb their nutrient from, a fluid the molecular concentration of which is altered by an increase in extractives and by unusual organic combinations of purin bodies. It is not difficult to conceive that such cells must work at high pressure in order to obtain their adequate intake and maintain their average output, or they must possess some inherent adaptability to the altered conditions of existence. If this be granted, for sake of argument, it lies near to hand to think that the constant overwork tends to shorten the life of the cell—in other words, to accelerate senile changes. Under these circumstances, it is but fair to suppose that the average cell becomes hypersensitive to certain stimuli and hyposensitive to others, and progresses to a stage of instability in action and response. Perhaps it is a little strange to imagine a glandular or a connective-tissue cell working under stress, and becoming unstable in its everyday output; but an unstable nervous system and nerve cell is already a possible entity in the minds of many. The neurotic patient is often described as highly strung, ill-balanced, etc. The cause, it is said, lies in the nerve processes,

in their connections with one another, in their hereditary capacities, the part played by the nucleus being frequently neglected. Why should the glandular and connective-tissue cells differ from the nerve cells? They live the same type of social life and exhibit interdependence. Why should they not also feel the wear and tear, and stress and strain? If the exhaustion or ill-balance of the nerve cell is manifested by delayed conductivities or slow response, then that of the gland cells might be shown by delayed or incomplete metabolism, and that of the connective-tissue cell by hypersensitiveness or delayed reactions.

There are many who classify gout as hereditary and acquired. Has the time not come when the latter term should be abandoned? Is there such a thing nowadays as acquired gout? Is it not rather that food and drink, etc., throw additional burdens on cells already overstrained, and thus accentuate an hereditary condition? Precise inquiry into the paternal or maternal history of the so-called "acquired" gouty patients in nearly every case reveals the possibility of an hereditary taint. The acute gouty paroxysm may be due to the action of toxic material upon cells whose resistance is temporarily lowered. There is much to be said for this view. The reaction and the temperature indicate the severity of the irritant, but whether these febrile attacks are really part of the gouty condition, or whether they are incidents arising from an external cause which acts in a certain manner upon hyper-irritable tissues, must not be considered as settled beyond possibility of doubt. Perhaps it is right to regard the paroxysm as the volcanic outburst; but the evidence connecting the outbreak with the underlying systemic disturbances is far too inconclusive to permit of dogmatism. In some patients the acute attack happens very rarely, and bears little or no relation to the intensity of the uricæmia or to the formation of tophi. It may even promote the absorption of tophi. Perhaps the paroxysm is really a secondary infection, and is a complication rather than the essential feature. The neuralgias, migraine, cardio-vascular conditions, and early senility, may all be occasioned by the hypersensitiveness and instability of cellular action. In such a case the defective activities of the vascular tissues may throw additional work on the heart and call for hypertrophy, while the earlier onset of senile changes in the cells of the bloodvessels, glands, and kidneys, would be associated with a progressive replacement or compensatory fibrosis.

The part played by the sexual glands in gout is not yet fully understood. Gout is rarely "declared" before the sexual functions are fully matured, and it is affirmed that gout does not occur when castration has been performed. In women gout is rarely met with before the menopause, but after this period women are subject to gout in a severe form. Yet the maternal transmission of gout is undeniable. Hippocrates explained these

facts by the nervous exhaustion consequent upon exercise of the male sexual functions, and by the discharge of some irritant substances with the catamenial flow. This nervous exhaustion means that the tissue cell, relieved of adequate nerve control, becomes inefficient or unstable. With women the case must be otherwise. In some way or other, during their period of reproductive activity they are secured against goutiness; when this period is over, their liability to gout is increased. Does not all this suggest that there is some deep underlying principle involved, and that the sexual secretions, internal or external, which preserve and transmit family tendencies, may play a part?

While the statement of these considerations may in no sense be considered as the outlines of an hypothesis, it at least constitutes an attempt to get behind the alterations in the metabolism of nucleins, behind the fermentative changes in the nuclein derivatives, behind even that toxin or organism which is accredited as the causal factor. A time will come when more is known of the exact nature of the inner processes of cell life, and then our views upon these difficult questions will rest on the surer foundations of tangible evidence.

The following summaries contain details of experiments and literature:

*Rose Bradford:* Allbutt and Rolleston's Medicine, 1907, vol. iii.
*Futcher:* Osler and McCrae, Medicine, 1907, vol. i., p. 848.
*Taylor:* Osler and McCrae, Medicine, 1907, vol. i., p. 266.
*Von Noorden and Walker Hall:* Metabolism and Practical Medicine, vol. iii.
*Luff, A. P.:* Gout, 3rd edition, 1907; Practitioner, July, 1903; July, 1909.
*Voit, F.:* Deutsche Klinik, 1909, p. 229.
*Umber, F.:* Therapie der Gegenwart, February, 1909.
*Schittenhelm, A.:* Medizinschen Klinik, 1907, iii., Heft 4.

## CHAPTER XIX

# PHYSIOLOGY AND PATHOLOGY OF THE KIDNEY

By J. H. RYFFEL

The principal function of the kidneys as excretory organs is to keep approximately constant the concentration in the blood of the various non-volatile crystalloid substances that are normally present, and to remove those that are abnormal. The waste products, such as urea, which are being formed continuously, are excreted continuously, but other substances, such as dextrose, are excreted only when present in excess. To perform this function efficiently, it is necessary that in an emergency the kidneys shall be capable of doing more than is ordinarily required of them, and that they shall be able to excrete in the urine those substances only which they are required to remove. Thus, in general the urine contains urea and chloride in considerable quantity, but only traces of sugar and protein. The power of selective excretion, however, is by no means perfectly developed when the substances involved are closely related, as in the case of bromide and chloride, which are excreted practically indiscriminately. The normal kidney can also within wide limits vary the amount of water it excretes independently of the substances in solution.

**The Formation of Urine.**—Before considering the limitations of these functions that occur as a result of pathological changes, it will be well to consider what is known of the processes by which normal urine is formed.

Two principal views have been elaborated as to the formation of urine. According to the one, the glomerulus and tubule both form urine, that from the tubule being more concentrated than that from the glomerulus; according to the other, the tubule is supposed to reabsorb water and other substances, such as sugar, from the dilute urine obtained from the blood by the process of filtration in the glomerulus. The latter view has been finally shown to be untenable by the experiments of Nüssbaum (24), and of Bainbridge and Beddard (3), in which urine was obtained from the kidneys of the frog when there was no circulation through the glomeruli.

Although the tubules have thus been shown to be capable of forming urine, it by no means follows that there is no part of the tubule which is reabsorptive in function.

Barcroft and his co-workers (5, 7) have shown that the action of certain substances—urea, sodium sulphate, and caffeine—in causing diuresis is attended by an increased absorption of oxygen by the kidney, whilst Ringer's solution and strong (5 per cent.) sodium chloride solution, when injected into the blood, cause marked diuresis without increasing the rate of absorption of oxygen. Moreover, when the kidney cells have been poisoned by means of mercuric chloride so that their consumption of oxygen falls practically to zero, solutions of sodium chloride still cause diuresis, while sodium sulphate solutions have lost their specific action, and cause merely a slight flow of urine, presumably due to salt action; and, finally, after the use of mercuric chloride, and when the blood has been much diluted with Ringer's solution, the concentration of chloride in the urine and the osmotic pressure of the urine are approximately equal to those of the blood (31). Hence they conclude that, whereas urea, etc., are specific diuretics exciting the kidney to secrete, solutions of sodium chloride act merely by diluting the blood and causing vaso-dilatation in the kidney (15, 25), and make their way into the urine by a passive process closely analogous to filtration. This process will for convenience be called "filtration." It is not, however, contended that the living cells through which it takes place have no influence upon it, but merely that, as it is not accompanied by increased absorption of oxygen, the cells involved are not doing an appreciable amount of work, so that the substances in the liquid produced must be present in approximately the same concentration as in the blood from which it is formed. Although this filtrate contains no coagulable protein, it otherwise closely resembles lymph and peritoneal fluid, and, as with these fluids, its formation is largely dependent on vascular conditions and the pressure within the capillaries. The specific diuretics, besides exciting a secretion, also cause vaso-dilatation in the kidney and thus increase the formation of filtrate, as shown in the experiments of Cushny (15), in which injection of sulphate and of urea both caused an increased output of chloride in the urine. Sulphate and urea are present in both the filtrate and the secretion, but mostly in the secretion, while chloride, as it fails to excite secretion, is present mostly in the filtrate. That this method of elimination of chloride is efficient is due to the relatively high concentration of chloride in the blood.

If these two processes, filtration and secretion, took place alone, the urine could contain as much chloride as the blood, or less, but never more. Now, human urine frequently contains 0·8 per cent. Cl, while human blood-plasma contains about 0·38 per cent. Cl, and the urine obtained as a result of injecting Ringer's

solution intravenously into rabbits may contain twice as much chloride as the blood at the time (9), so that to render this view of the production of urine complete it is necessary to add a third process: that of reabsorption of water from the urine already formed by the other two processes. Reabsorption of water would involve work by the cells of the kidney, as the urine is thereby concentrated, and should therefore involve some absorption of oxygen. It takes place only when the kidney is alive and is taking up oxygen continually, but it is not increased when diuresis is produced by means of sodium chloride solutions, so that as the diuresis passes off the concentration of both chloride and urea in the urine rises (9).

The three processes together would not be calculated to yield urines in which the concentration of chloride was very much greater than that in the blood, and this is found actually to be the case, as the chloride of the urine is practically never more than three times as concentrated as that of the blood, and this concentration is approached only when the flow of urine is not great. On the other hand, urea, which is secreted, may be a hundred times as concentrated in the urine as in the blood. If this criterion of concentration is applied, phosphate, creatinin, pigment, and sugar when excreted, as well as urea and sulphate, must all belong mainly to the secretion. Macallum and Benson (21), by drinking large quantities of distilled water, obtained copious urine containing as little chloride as 0·03 per cent., when the blood was but little altered in composition, so that the kidney cells would appear also to be able to secrete water.

That this view of the formation of urine is absolutely correct has not been proved, but it is in accordance with known facts, so that we are justified in applying it to the elucidation of pathological problems. The processes involved are three: Filtration, by which water and chloride mainly are eliminated; secretion, by which water, urea, sulphate, and other substances, are eliminated; and reabsorption, mainly of water. As to the regions of the kidney tubule which execute these different functions, it is reasonable to assign reabsorption to the lower part of the tubule. We know that some part of the tubule, as opposed to the glomerulus, presumably the first convoluted tubule, can secrete urea in the frog (4, 14). The formation of filtrate has usually been assigned to the glomerulus, probably without sufficient reason. The disposition of the circulation favours this idea, as owing to the intervening vas efferens the pressure in the capillaries of the glomerulus must, when the blood is flowing, be higher than that in the capillaries that surround the tubules; but evidence which may bear a contrary interpretation will be discussed under experimental nephritis. Brodie has suggested for the glomerulus another function, that of a pulsating hammer which serves to drive the contents of the tubule forward at each cardiac systole.

Suzuki (28) has recently made some interesting observations on the elimination by the kidneys of carmine injected subcutaneously into rabbits, guinea-pigs, cats, and other animals. If the animal is killed during the excretion of carmine, cylinders of finely granular carmine are found in the lumen of the collecting tubules, but only a little carmine in the lumen of the first convoluted tubules. If the dose is large, and the animal is not killed too soon after the injection, red granules are seen in the cells of the first convoluted tubules, and nowhere else. These granules are not stain in process of elimination, as they do not appear as soon as excretion begins, and they persist some time after it has ceased; but they afford evidence that stain passes through the cells. Occasionally with large doses a little stain is seen within the capsules of the glomeruli. Suzuki concludes that carmine is excreted mainly by the first convoluted tubule, and that the concentrated stain seen in the lumen of the collecting tube is not due to excretion of stain in the distal tubules, but to reabsorption of water, probably by the second convoluted tubule. His results thus afford useful confirmation of the theory proposed above, but they afford no evidence as to the function of the glomerulus, since the small amount of stain seen in the glomeruli may have regurgitated from the adjacent tubule.

**Influence of the Circulation on the Flow of Urine.**—All observers are agreed that, other things being equal, the rate of formation of urine depends on the rate of the flow of blood through the kidneys. When the arterial blood-pressure is constant, vaso-dilatation increases, and vaso-constriction diminishes, the flow of urine. When the state of the arterioles is constant, the flow of urine is increased by a rise of arterial pressure, and diminished by a fall. If, when the arterial pressure is constant, the venous outflow is impeded, the flow of urine is reduced, and when the vein is completely blocked the formation of urine ceases (16). This holds for excised kidneys perfused with 1 per cent. salt solution as well as for the kidneys in the body (27). The elimination of water and chloride is more affected by such vascular variations than is that of urea, etc.

**The Internal Secretion of the Kidneys.**—Various attempts have been made to show that the kidneys have an internal secretion. Thus, the kidneys of animals have been removed, and the effect of subcutaneous injection of renal extracts on the duration of life and symptoms of the animals observed. Extracts of kidney and the blood coming from the kidneys have been found to raise the arterial blood-pressure. The observations are, however, inconclusive (8). Rose Bradford removed a wedge-shaped piece of the one kidney, and later the other kidney, and found that, when the remaining kidney tissue amounted to less than one-third to one-fourth of the original total kidney substance, the dogs had an increased nitrogenous metabolism, and wasted rapidly. Bainbridge and Beddard, how-

ever, repeated the experiments on cats, and came to the conclusion that the increased output of nitrogen came on only a short time before death, and that the effects observed could be explained by inanition, as the animals refused food. We may conclude, therefore, that there is no evidence of an internal secretion on the part of the kidneys.

**Polyuria—Diabetes Insipidus.**—In nervous excitement, hysterical and emotional states, or as a result of lesions affecting the pons, cerebellum, or medulla, the urine passed may for a time be both copious and dilute, so that the hourly output of total solids is but little altered. In these conditions both pulse-rate and arterial blood-pressure are usually above normal, so that when the kidneys are normal the main factor in causing polyuria is probably vascular, the flow of blood through the kidney being above normal. Other suggestions are that there is an overproduction of pituitary secretion, the natural diuretic of the body, or that the nervous excitement activates secretory nerves of the kidney; but these nerves have never been proved to exist.

In diabetes insipidus there is permanent polyuria without any corresponding error in metabolism or gross lesion in the kidneys. The symptom may appear suddenly, but when it has once begun it is permanent. The urine is normal, except that it is dilute, and therefore the daily volume is greater. Meyer (22) has investigated the condition; he finds that it is impossible to remove the polyuria by restricting the water taken, as the resulting thirst is too great. On the other hand, a diet without meat and with a minimum of sodium chloride greatly reduces the polyuria. Addition of sodium chloride to the diet increases it, but sodium phosphate does not. He concludes that in this condition the kidneys are unable to form a concentrated urine, so that in order to remove waste products the volume of the daily urine is increased. The greater the amount of soluble products to be eliminated, especially sodium chloride, the greater the daily volume of urine. Diminished reabsorption of water would account for the facts, but there is no proof that this is the explanation.

**Albuminuria.**—Normal urine contains practically no protein. When coagulable proteins are present in quantities that can be detected by ordinary tests, the phenomenon is known as "albuminuria." The urine from a normal kidney becomes albuminous when the renal artery is partly obstructed, so that the supply of blood is greatly reduced, but not entirely cut off. Partial obstruction of the renal vein produces the same result, and blood and hyaline casts also appear in the urine if the obstruction is maintained for a considerable time. When the vein is completely occluded for a short period, albumin and blood first appear in the loop of Henle, and later in the capsule of the glomerulus (12). Clearly, then, a

diminished supply of blood to the kidney is a cause of albuminuria. Araki (1) found albumin in the urine of animals which had been kept in an asphyxial condition for considerable periods either by limiting the supply of oxygen or by the use of carbon monoxide, so that lack of oxygen is probably a factor in the effect of diminished circulation. Another cause of albuminuria—the action of certain poisons on the kidney cells—will be discussed under Nephritis. The coagulable proteins that occur under these conditions are always apparently identical with the albumin and globulin of blood-serum. Now, foreign proteins, such as egg albumin, when present in the blood, are excreted by the kidneys, so that it is possible that the proteins of some cases of albuminuria may be foreign proteins excreted by the kidneys, or may be the albumin and globulin of the plasma excreted in association with some foreign or toxic substance.

*Albuminuria after Hard Exercise.*—Temporary albuminuria occurs after continued hard muscular exercise. This is apparently universal provided the exercise be sufficiently violent and continued for a sufficient period (13, 2). In hard exercise there is at first a marked rise of arterial pressure. This gradually passes off as the exercise is continued, and is followed during the subsequent period of rest by a marked fall of blood-pressure, if sufficient fatigue has been induced. According to Dr. Armstrong (2), the albuminuria of exercise occurs only in those cases in which there is a definitely subnormal arterial blood-pressure in the period after the exertion. At the same time hard exercise leads to dilatation of the right side of the heart and distension of the liver, so that there is some venous engorgement as well. It is thus very probable that the cause of the albuminuria is a deficient supply of blood to the kidneys, owing partly to vaso-constriction in the kidneys, partly to low arterial pressure, partly to venous congestion. This view is confirmed by the occurrence of a marked fall in the chloride of the urine as a result of hard exercise even when albuminuria does not occur. It is possible, however, that the proteins of this albuminuria may be toxic substances produced as a result of the exertion and excreted by the kidneys.

*Orthostatic Albuminuria.*—Certain otherwise normal individuals have albuminuria when they are in the erect posture, but not when they are in bed, or even when sitting. In one case albuminuria occurred when the patient was placed on a board and inclined to the horizontal at an angle of 40° or more, but did not occur even in the erect posture when he wore pneumatic trousers with a pressure of 50 millimetres of mercury (17). Probably this condition, like the albuminuria of hard exercise, is caused by diminished circulation through the kidneys, due in this case to the effect of gravity on the circulation.

*Albuminuria in Heart Failure.*—In cases of heart failure albumin-

uria frequently occurs without any gross pathological lesion existing in the kidneys. Whether there is albuminuria or not, the urine is small in amount, and contains a considerable quantity of urea, but relatively little chloride. The power of excreting water and chloride is considerably diminished, and œdema is frequent. When a diet nearly free from chloride is given, the œdema tends to diminish (20), indicating that retention of chloride is the cause of the œdema. In heart failure there is obviously an inefficient arterial blood-pressure, together with a certain amount of venous congestion, so that it is clear that the circulation through the kidney must be considerably diminished. Probably this is the cause of both the albuminuria and retention of chloride.

A somewhat analogous condition occurs during normal sleep. The arterial blood-pressure and the rate of the circulation are both diminished. There is no œdema or albuminuria, but the urine is usually concentrated as regards urea, and contains relatively little chloride. Thus, on an ordinary diet the urine secreted during sleep in bed amounted to 25·5 c.c. per hour, and contained chlorine 0·101 per cent., 0·026 gramme per hour; urea 2·87 per cent., 0·73 gramme per hour. Urine secreted immediately after rising, without taking food or drink, amounted to 37 c.c. per hour, and contained chlorine 0·527 per cent., 0·195 gramme per hour; urea 2·28 per cent., 0·84 gramme per hour. If water was taken on rising, the volume of urine and excretion of chloride were both increased, but the urea was little affected. When extra chloride was taken before going to bed, the chloride excretion showed similar variation, but the actual figures were higher.

**Hæmaturia.**—Blood in the urine is recognized by the presence of red corpuscles. It is the result of some break in continuity in the walls of the bloodvessels of the glomeruli or tubules of the kidney, or anywhere in the urinary passages. It occurs as a result of mechanical injury, in hæmorrhagic diseases and septic conditions, as a result of the presence of tumours or calculi, and, finally, in the different forms of nephritis. Hæmaturia, from which, apparently, complete recovery may take place, also occurs in certain cases without assignable cause. These are probably manifestations of a general tendency to hæmorrhage in various parts of the body, which is especially noticeable in the members of certain families.

**Hæmoglobinuria** is distinguished from hæmaturia by the absence of red corpuscles from the urine, and by the relatively small amount of coagulable protein present. If the urine is alkaline owing to the presence of ammonia, hæmaturia may simulate hæmoglobinuria, the corpuscles being laked by the ammonia. Hæmoglobinuria is due to the presence of free hæmoglobin in the plasma, which is excreted by the kidneys. It occurs as a result of the action on the blood of hæmolytic substances, such as ether, potassium chlorate,

and hæmolysins. Paroxysmal hæmoglobinuria is due to the presence of hæmolysin in the blood (p. 17).

**Experimental Nephritis.**—Various poisonous substances when injected subcutaneously into animals cause the appearance of albumin, blood, and casts, in the urine, and produce degenerative changes in the tissues of the kidney. These substances are divided into two classes: (1) Those, like uranium salts, potassium bichromate, and mercuric chloride, which act mainly on the first convoluted tubule, so that with limited doses no change is seen in the glomerulus; and (2) those, like arsenic and cantharides, which act primarily on the glomeruli, producing inflammatory changes therein and desquamation of epithelium. Uranium is apparently the most specific of these poisons, in that doses which produce definite necrosis in the tubules of the kidney cause very little change in other organs. The action of arsenic and cantharides is certainly not limited to the kidney, and that of cantharides is in the kidney not limited to the glomerulus, as it causes necrosis of the first convoluted tubule as well (28). In the action of the first group there is usually only slight hæmaturia, and the albumin comes mainly from the tubules; in the second hæmaturia is more marked, and the albumin comes mainly from the glomeruli.

Schlayer and his co-workers (25) compared the reaction of normal kidneys to sodium chloride, caffeine, and adrenalin, injected intravenously under an anæsthetic, with that of kidneys poisoned with members of the first and the second groups respectively. Under the action of the first group the blood-pressure was well maintained, and the vascular reactions, vaso-dilatation with sodium chloride and caffeine, and vaso-constriction with adrenalin, and the flow of urine, were at first as great as normal. In later stages or with larger doses of poison the diuresis and vascular reaction both failed ultimately, but the diuresis failed first, so that kidneys were obtained which still gave a good vascular reaction, but failed to produce urine. Diuresis produced by sodium chloride failed before that with caffeine, but, as the chloride was always tried first, this observation is not reliable (9). The fact remains, however, that caffeine can produce greater diuresis for a given vascular reaction than can salt solution. Under the action of the second group the blood-pressure was low, and there was marked failure of both diuresis and vascular reaction. They also found that without anæsthetic the first group, especially uranium, diminished the power of excreting chloride and iodide, but not that of excreting milk-sugar. Similar experiments with the second group were rather unsatisfactory, owing to the rapid death of the animal; but apparently the power of excreting milk-sugar was greatly diminished, while the percentage of chloride and iodide in the urine that was obtained was as high as normal. They concluded that chloride and iodide are eliminated by the tubules, and milk-sugar by the glomeruli, and

that examination of the excretion of these substances affords an indication of the nature of the lesion. These conclusions are probably not justified. The substances of the uranium group ultimately cause complete suppression of urine. Suzuki (28) has shown that, when urine is still obtained, only part of the first convoluted tubule is destroyed, which, since a third of the normal kidney tissue is sufficient for excretory purposes, would probably leave enough first convoluted tubule to excrete milk-sugar efficiently. As to the second group, there is always considerable reduction of the amount of urine, and the changes seen in the glomeruli—hyperæmia and desquamation of epithelium—do not justify the conclusion that the glomeruli give a filtrate with difficulty, but only that this filtrate contains blood and albumin, so that the high figures for chloride in the urine that were obtained do not lead to any definite conclusion.

Boycott and Ryffel have recently studied the effect of uranium-poisoning on the response of the kidneys to diuretics, in anæsthetized animals. Their results differ from those of Schlayer in that the change in the response to caffeine, Ringer's solution, and strong salt solution is of a similar order. The urines obtained from the nephritic animals are in general less in volume, and contain definitely less salt and urea than those obtained by similar treatment of normal animals. Moreover, in the nephritic, as the diuresis passes off the concentration of chloride in the urine either falls or remains stationary, while that of urea rises; in the normal, the concentrations of both urea and chloride rise, unless much sugar is present, when the chloride may fall. Sugar, which is present in the urines of both normal and nephritic animals, is due to the anæsthetic and to operative interference. The concentration is greater in the normal. These results, as do those of Schlayer for uranium, point clearly to diminished production of chloride-containing filtrate. Now, the glomerulus is apparently normal in uranium nephritis, so that either the filtrate does not come from the glomerulus, or the glomerular epithelium has undergone a change not visible histologically, whereby the production of filtrate is impeded. We are not, therefore, justified in assigning the function of production of filtrate to the glomerulus until the apparent discrepancies seen in experimental nephritis have been explained.

**Nephritis (Bright's Disease).** — Both glomeruli and tubules are always affected in nephritis which is not due to special causes.

The functional activity of kidneys affected by the various forms of this disease has been tested in a number of ways:

1. The patient is given a diet the quantity and composition of which are exactly known. The composition of the twenty-four hours' urine is then determined as to water, chloride, phosphate, sulphate, and total nitrogen (23). Provided there is no marked destruction or building up of tissue taking place at the time, it can thus be shown whether there is a lack of any normal

constituents of the urine. The deficiency of any of these substances in the urine does not prove that they are being retained to any extent in the body, as they may be eliminated in other ways, notably in the sweat; but it does show that the kidneys fail to excrete them. This method is laborious when applied fully, but a modification of it is used to investigate the excretion of chloride, as it is the only method available. To do this the patient is first given a fixed diet, containing a known small amount of chloride, preferably milk or milk and farinaceous materials. When equilibrium is attained, either a single dose of sodium chloride—say 10 grammes—is given, or a known amount of chloride is added to the diet. The chloride in the urine is determined, and the patient is weighed daily to ascertain whether water is being retained. In general, retention of chloride and of water take place together. This may or may not be accompanied by visible œdema.

2. Foreign substances are given—for instance, methylene blue, potassium iodide, lactose—and their excretion is studied. Schlayer (26) observes the elimination of sodium chloride and potassium iodide given by the mouth, and of lactose injected intravenously. The usefulness of this procedure for diagnostic purposes naturally depends on the accuracy of his conclusions from his experiments on experimental nephritis.

3. The freezing-point of both urine and blood is determined as a measure of the concentration of molecules and ions therein.

4. The concentration of urea or of non-coagulable nitrogen in the blood or blood-serum is determined. If the urea is above normal limits, there is not necessarily progressive retention of urea within the body. The kidneys and the skin may be excreting as much as is being formed, but the kidneys are in this case excreting urea inefficiently, as they require more than the normal stimulus. Estimation of urea in serum in conjunction with a study of the elimination of chloride has been extensively used, notably by Widal and Javal (29). It is necessary to know how much protein the patient is taking, as this affects the result. Thus, a woman who was fed on milk containing 105 grammes protein per diem had 1·2 per 1,000 urea in her serum. When her diet was changed to a vegetable one containing 28 grammes protein per diem, the urea fell to 0·36 per 1,000, and again rose to 0·57 per 1,000 on a diet containing 64 grammes protein per diem. The normal limits are given as 0·15 to 0·5 urea per 1,000 parts of serum. Widal and Javal's general conclusions are embodied in the following account.

*Acute Nephritis.*—The urine in this condition is small in quantity, contains albumin, blood, casts, urea, usually in considerable concentration, but relatively little chloride. Œdema and retention of chloride occur frequently. There is an increase of the urea of the blood, but this is usually not great unless there is almost complete suppression of urine. The kidneys are in a condition of acute

inflammation; they are large, the bloodvessels are gorged with blood, the lymph spaces dilated. Glomeruli may be seen so much swollen that the capsular space is obliterated. Presumably, as with other inflamed tissues, although the vessels are dilated, the flow of blood through the organ is less than normal, owing, apparently, to increased frictional resistance offered by the walls of the vessels. The diminished circulation and the inflamed condition of the cells both contribute to the diminished production of filtrate and retention of chloride. Urea, on the other hand, forming part of the secretion of the tubules, is more efficiently eliminated as long as the cells of the tubules are in any way capable of exercising their excretory function.

The inflammation is almost certainly not due to bacterial infection of the kidney itself. It must therefore be due to toxic substances which reach the kidney by the blood-stream. As these substances must be produced somewhere, acute nephritis is to be regarded rather as the result of disease occurring in other parts of the body than as a disease in itself.

*Chronic Nephritis.*—Cases of chronic nephritis may be divided into two main groups. In the first group there is difficulty in excreting water and chloride, and there is frequently œdema, which is reduced by limiting the chloride in the food, but the urea of the blood is not increased. The urine is in fairly good quantity, contains albumin and casts, and may contain blood, which comes usually from the glomeruli. It contains a fair amount of urea, but relatively little chloride. On histological examination it is seen that much functional kidney tissue still remains. The vessels of the kidneys contain little blood. The lymph spaces are dilated. Cells in both glomeruli and tubules show necrosis and desquamation. In the glomeruli adhesions are forming between the glomerulus and its capsule (19). Presumably the tissue pressure in the kidney is high and the circulation poor. This contributes to the malnutrition of the kidney, and is the main cause of the diminished production of filtrate and retention of chloride. This condition follows on acute nephritis when the reparative changes are not efficient, and is often described as "large white kidney." As regards the functional disturbance in the kidney, it resembles heart failure with albuminuria, and, like it, is improved when the circulation improves; but the requisite arterial blood-pressure is higher in nephritis, as some permanent damage of kidney tissue has already taken place.

In the second group the urea of the blood is increased above normal limits, showing that the secretory power of the kidney is diminished. The kidneys are contracted and contain a considerable amount of fibrous tissue, so that, clearly, the amount of tubular tissue is considerably diminished. In some cases up to the last stages the daily amount of urine is as great as, or greater than, the normal, but it is always dilute. Although the percentage of chloride

is never high, there is no great difficulty in excreting chloride. There is no œdema or retention of water. The urine contains little albumin, few casts, occasionally blood, especially in the last stage. The arterial blood-pressure is high, and the kidneys are vascular. Some glomeruli and tubules are clearly functionless; others are clearly functionating, but the tubules are dilated and their epithelium flattened, while the glomeruli may be contracted (19). In other cases the urine is dilute, but its quantity is usually not greater than normal, and may be considerably less. It contains albumin and casts, sometimes blood, relatively little, or occasionally only traces of, chloride. Excretory power for chloride is very considerably diminished, so that œdema and retention of water and chloride may be marked. These cases differ from the previous ones in that the circulation through the kidneys is poor, so that post mortem the kidneys are pale as well as contracted. More active changes are also visible in the cells of the tubules and in the glomeruli.

We have to consider the question why in this second group the urine is always dilute, and why there is difficulty in excreting urea, pigment, etc. Rose Bradford (10) removed one kidney and excised a wedge-shaped piece of the other kidney in dogs. If the remaining kidney tissue was not less than one-third of the normal, the dog suffered no ill effects, except that the urine was usually dilute, so that the daily volume was increased. The remaining tubules were normal, but they were overworked and the current of urine in them abnormally great. The opportunity for reabsorption of water by the lower part of the tubules was therefore diminished, as it is in diuresis. It is difficult to believe that the reduction of kidney tissue in contracted kidneys is ever as great as in these experiments, but the tubules are never normal. Even in those cases where there are very few casts and little albumin, the epithelium is flattened, so that secretory power is certainly diminished. Hence the secretory failure in contracted kidney is due to a combination of the reduction of kidney tissue and the abnormality of the tissue itself.

**The Kidneys in Arterial Disease.**—Whether the disorder is senile arterio-sclerosis, or the one which occurs in younger people and produces the condition known as "reine schrumptniere,"* the changes in the kidneys are the result of a general disease of the arteries, which affects other parts of the body as well, especially the brain (19). Branches of the renal arteries undergo gradual obliterative changes. As the blood-supply is reduced, this leads first to a reduced production of filtrate and albuminuria, later to complete cessation of function in the part affected. Since the change is much more advanced in some branches of the renal arteries than in others, the glomeruli and tubules supplied by one branch are obliterated, while those

* There is no accepted English term for this condition. The translation of the German term is "genuine contracted kidney."

supplied by another branch are practically normal. The functional activity of the kidneys naturally depends on the amount of normal or nearly normal tissue remaining.

**Obstruction to the Urinary Passages—Hydronephrosis.**—Obstruction to the urinary passages by impacted calculi, stricture, enlarged prostate, etc., produces one of two results: either the kidney atrophies without producing much dilatation, or secretion continues and the ureters, pelvis and tubules of the kidney are gradually dilated, the kidney becoming ultimately atrophied so that nothing remains but a sac containing a dilute fluid resembling urine. In general, complete obstruction results in direct atrophy, while partial obstruction causes hydronephrosis. The determining factor is whether the kidney continues to secrete or not. If it does, the tissues are exposed to a continuous tension, due to the pressure of the urine. This pressure is not very great—50 to 60 millimetres of mercury as a maximum in dogs; but the tissues involved are not true solids, so that they undergo a gradual stretching, the magnitude of which is determined by the stretching force and the time during which it acts. As this process involves atrophy of kidney substance, the functional results depend on the amount of active tissue left. Kidneys which have partially undergone the process, become contracted when the obstruction is removed.

When one ureter is obstructed experimentally, the result depends on the pressure involved: when the pressure is low—about 10 millimetres of mercury—the obstructed kidney may at first yield more urine than the normal kidney (11); when the pressure is greater—15 to 30 millimetres of mercury—the obstructed kidney always yields less urine, which is at first more concentrated as to sulphate, urea, pigment, than that from the normal kidney, and even the chloride is more concentrated, when sodium chloride is used as the diuretic (15). The dilute urine obtained in hydronephrosis is therefore to be attributed to the atrophy of the kidney, and not to the direct effect of the obstruction on a normal kidney.

**Functional Disturbance of the Kidneys in Other Conditions.**—The results of tumours, cysts, lardaceous disease, embolism, calculi, and of bacterial infection, depend on the amount of active kidney tissue left. In embolism of the kidneys, whether septic or not, the urine contains much blood, which comes mainly from the glomeruli. Where the kidneys are unequally affected, as may be the case in ascending septic nephritis, the urine from the affected kidney is frequently less in quantity and more dilute than that from the normal, but occasionally the output of chloride from the affected side is much less diminished than that of urea.

**Uræmia.**—When the kidneys are contracted or the effective amount of kidney substance is greatly reduced, the patient may

continue to live for a considerable time with an abnormally high quantity—nearly 1 part per 1,000—of urea in his blood. If, owing to further toxic processes or to failure of the circulation, the activity of the kidneys is reduced, uræmia supervenes. This is characterized by a rise of urea in the blood, usually to from 2 to 4 parts per 1,000, and by various nervous symptoms—vomiting, convulsions, coma, paralyses, hyperpnœa, or Cheyne-Stokes respiration. If, however, there is more sudden and complete failure of the kidneys, as may happen in acute nephritis, or from obstruction of the urinary passages, from embolism, or in animals from removal of the kidneys, death takes place usually more quietly from a gradual onset of coma without convulsions, although the urea of the blood rises usually higher than in typical uræmia. Of thirty-six cases of complete anuria quoted by Osler, all lasted more than four days, and seven lasted more than fourteen days. In some of the cases there were muscular twitches, but convulsions were rare.

The causation of the symptoms of uræmia has been much discussed, on the supposition that they were due to the presence of some toxic substance in the blood, but not one of the ordinary excretions of urine has been found sufficiently toxic. Feltz and Ritter (18), however, obtained results suggestive of uræmia by injecting urine into the circulation of animals. Another suggestion is that toxic substances formed in the inflamed kidneys are the cause of the uræmic symptoms, but if this were the case we should expect more marked symptoms in acute nephritis than in the more gradual failure of contracted kidneys, and the fact that in uræmia the urea of the blood is always increased, though to a variable extent, favours the conclusion that the symptoms are the result of retention of excretory products. That the symptoms of complete retention should differ to a certain extent from those of partial retention is not surprising, since in the former all the excretory products accumulate as they are formed except in so far as they are excreted by organs other than the kidneys; while in the latter, since the kidneys act to some extent, we should expect some substances to be excreted better than others.

The symptoms of uræmia strongly suggest lack of oxygen in the brain. The blood is not remarkably poor in oxygen, but Barcroft and Camis (6) have shown that the addition of salts and other soluble substances to hæmoglobin alters very markedly its dissociation curve, so that it is possible that in the presence of accumulated excretory substances the oxygen of the arterial blood is not properly available.

**Eclampsia.**—Pregnant women, who before pregnancy were apparently free from kidney disease, may develop symptoms suggestive of uræmia: headache, œdema, visual disturbances, epigastric pain and vomiting, and, finally, convulsions and coma. The urine

contains albumin and casts, and sometimes blood, and is reduced in amount, but usually concentrated. Bile pigments and an increased proportion of ammonia are frequently present, and sometimes the acetone bodies and lactic acid, though the latter is to be attributed directly to the convulsions. Post mortem the kidneys show changes, especially in the tubules, not unlike those seen in uranium-poisoning; but hæmorrhages, cloudy swelling, and necrosis are to be seen in other organs as well, notably in the liver and brain. There is undoubtedly a certain amount of failure of kidney function, but this is to be attributed to a toxæmia, probably of placental origin, which affects other organs as well (30).

On the other hand, when the kidneys are previously damaged by disease, pregnancy affects them adversely, so that an aggravation of symptoms and uræmia may result.

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## CHAPTER XX

# DEATH

By JAMES RITCHIE

DEATH, the natural termination of life, might be looked for when the cells of the body, by a gradual process of decay, failed to maintain the exchange of material which is characteristic of life. The body, however, is so complicated that death from such a pure condition of senility occurs but rarely, and not more than 5 per cent. of the population of Great Britain die under circumstances which warrant the assignment of old age as the cause. Even if we confine our review to deaths due to disease, we find in the great majority of cases that death occurs either when the tissues have not reached their full maturity or while they still possess adult vigour. In nearly one-half of the total deaths in this country death is due to invasion by pathogenic bacteria, and in other cases is traceable to a pathological change in some tissue or organ of the body, causing a failure in function, and thus upsetting the equilibrium of the organism as a whole.

If we look more closely at the causes of death, we find, taking those traceable to infection, that certain age periods show special susceptibilities. Thus in early life the chief causes of death in Britain are pneumonia, measles, whooping-cough, and diphtheria. During the first thirty-five years of life tuberculosis plays a prominent part in death, and during the whole of adult life, but especially in its prime, the mortality from pneumonia is a serious factor. Passing to the group of conditions where death is due to failure of function, we find the system most frequently at fault to be the circulatory, diseases of the heart and bloodvessels accounting for about 15 per cent. of the total death-rate. This cause operates especially in later adult life, and, still later, diseases of the respiratory system constitute a serious menace to life. In very early life the nervous system manifests considerable instability in the form of a special susceptibility to peripheral irritation. Thus a large number of cases of death from convulsions occurs. It is by the operation of such causes as those enumerated that so few individuals reach the period when a natural senility supervenes.

Great differences exist in what may be called the inherent fatality

of different diseases, and it is only in certain cases that, when a disease process is once started, a fatal issue can be the only result. As might be expected from the existence of an antagonistic mechanism in the body, recovery can be looked for in every form of infective disease, and in any particular case (*e.g.*, in typhoid fever) may occur even when the most serious effects have been produced on the bodily metabolism. On the other hand, in such diseases as diabetes and endarteritis, though a fatal issue may be long postponed, it is none the less certain.

In many cases death is the direct result of the disease, as where in an infection the heart is weakened, the kidney excretions are suppressed, or a profound degree of fever produced. On the other hand, death may be due to the secondary supervention of pathological processes other than those primarily present. Thus in many infections, such as diphtheria, typhoid fever, and measles, death is due to the superimposition of a pneumonic process; and in diseases which primarily are degenerations, a tendency to other affections may be manifest, an outstanding example being the proneness of diabetic subjects to suffer from bacterial invasion, leading to gangrene or tuberculosis. The secondary effects of disease in shortening life are often remote. Thus acute rheumatism may be completely recovered from so far as general disturbances are concerned, but the heart may be permanently injured, and, long after, death may result from its failure. The secondary effects causing death may even assume an accidental form, as when thrombosis occurs as part of the primary disease, and death results from a detachment of the clot.

If we inquire as to the events which lead up to death, we find a great variation in different diseases. To take first of all general diseases. In the important group of infections there are general effects produced on the brain, the heart, and the kidneys, which affect the co-ordination of these with other organs of the body. The effects are probably traceable to the little-understood toxic action of various infective agents by which the functional activity of the highly-specialized cells of the body is seriously interfered with. Here the disturbance of metabolism, of which fever is the expression, constitutes an important factor. Death thus produced by essential phenomena may be seen in any infective process, and is perhaps best exemplified in pneumonia. The serious changes resulting from infection may be complicated by secondary infections being superimposed upon a primary, as in the occurrence of pneumonia due to the pneumococcus, which is a serious factor in the fatality of measles, where another infective agent is acting as the primary cause. In certain infections life may be threatened by accidental complications, as is seen in typhoid fever, where the ulcerative processes in the bowel may lead to fatal hæmorrhage or perforation of the intestinal wall.

Of other general diseases which threaten life, malignant tumour formation is the most important. Here death may be due to the gradual weakening of all the bodily functions through the occurrence of cachexia, the precise origin of which is unknown. But the fatal effects of malignant disease are probably more often traceable to secondary conditions, such as pneumonia and septic processes. Death, here again, may be due to accidental conditions; for example, ulceration (leading to hæmorrhage, perforation of bowel, etc.), involvement of vital structures in the growth, blockage of natural passages, such as the larynx and alimentary canal, etc.

The general diseases affecting the organs of the internal secretion may also be referred to. In these, again, the weakening of all the bodily organs through the lack of the secretion may itself cause death. This occurs in certain cases of diabetes, in cases of thyroid inefficiency, and also probably in diseases of the suprarenal. In the last case waxy disease of the organ is sometimes associated with a progressive weakening of the heart, and this is also seen in the rare event of an apoplectic hæmorrhage disintegrating the suprarenal organ. In the general diseases associated with anæmia death is usually traceable to the changes in the heart following on deficient oxygenation.

We may now pass to look at the methods by which diseases of particular systems threaten life. In the circulatory system death may result from affections of both the central and peripheral parts. The functions of the heart are liable to interference from a great variety of causes. These include the intrinsic changes in its muscular structure, the development of defects as a consequence of inflammation of its valves, and defects traceable to its becoming unable to cope with increased calls on its energy, originating either in intrinsic valvular deficiencies or in extrinsic obstacles to its action, such as follow on the development of deficiency of elasticity in the arterial system of the body. The failure of the heart may be sudden or it may be gradual. The former is commonest where intrinsic muscular degenerations have long been in existence, where defects of the aortic valve exist, and in many cases the syncope may be due to the failure of the heart being reflected back upon itself through an insufficient supply of blood reaching the cardiac centre in the medulla. The slower types of cardiac failure may, again, result from intrinsic degenerations, but are specially characteristic of disease of the mitral valve. They are associated with deficiencies in the circulation, which result in œdema, and when this comes to affect the lungs, asphyxiation results. Cardiac disease may produce death from secondary effects, the most important being embolism. A vegetation may become detached from a cardiac valve, may lodge in vessels supplying vital parts of the brain, causing sudden death, or in the superior mesenteric artery, causing death from shock or from the reflex effects of pain; or if the emboli

contain organisms, they may originate multiple foci of suppuration all over the body, the immediately fatal effects of which are usually attributable to involvement of the kidneys or brain. Disease of the peripheral parts of the circulation may also be fatal, examples being found in the rupture of an aneurism arising from endarteritis, or the sudden derangement of the heart by the lodgment in it of a thrombus detached from a peripheral vein in which phlebitis has occurred. Though diseases of the respiratory system are responsible for so many fatal illnesses, death (*e.g.*, in pneumonia) may not result from direct interference with the respiratory function, but from the general effects produced in other systems. In many cases of bronchitis, however, a direct effect is produced, and death is due to asphyxia. Reference may here be made to the fatal effects of a sudden pneumothorax. These are probably traceable to a secondary involvement of the heart. In diseases of the brain death may be primary or secondary. In the case of the former it is sometimes associated with a slowly progressing general interference with nutrition, but, especially in the case of more rapidly developing morbid changes, originates in a rise in the intracranial pressure. This may occur in tumours, but it is specially well marked in cerebral hæmorrhage. It causes unconsciousness, sometimes prolonged, but the directly fatal effect probably results from a stimulation of the inhibitory mechanism in the cardiac centre. In long-standing brain disease death is often due to pneumonia arising from a lowered resistance of the pulmonary tissue, or consequent on the passage of food into the larynx, through dulling of the reflex which normally results in coughing. Where disease affects the spinal cord, death usually comes from secondary conditions, such as sepsis arising from bedsores or from infection of the bladder and kidneys, but disease high up in the cord* may act by producing hyperthermia, hypothermia, or respiratory failure due to paralysis. Fatal effects in disease of the peripheral nerves are traceable to similar causes, the affection of the respiratory muscles being again important. The direct cause of death is usually a low form of pneumonia.

Passing to the genito-urinary system, apart from sepsis, the most important conditions are acute and chronic inflammations of the kidney. In both there may be a suppression of the function of the organ, and consequent poisoning of the body from retention of what normally is excreted—the condition known as "uræmia." The precise factors at work in such an eventuality are not clear, but a toxic action on the nervous system, and the lowered vitality of nervous function generally, form important factors. In chronic kidney disease, besides the danger of uræmia, secondary effects having a tendency to a fatal issue may be found in certain cases in the constant drain of the albumins of the blood which occurs, and

* See p. 532.

in the secondary effects produced in the heart in consequence of the rise of blood-pressure, which practically always accompanies chronic nephritis. The terminal stage of kidney disease frequently presents itself in the form of œdema of the lungs of unexpected onset. The immediate cause of this incident in any particular case is usually not apparent, and seems to originate primarily from the kidney condition, and not from an already existing condition of cardiac weakness.

Diseases of the alimentary system play a considerable part in causing death. The functions of the system may be secondarily affected by a great variety of conditions, and the primary assimilation of food by the body may thus be diminished so as to lead to what amounts to starvation. The chief conditions in the system itself which threaten life are the development in it of malignant tumours. These affect its functions in a variety of ways. When arising in the œsophagus or stomach, they may cause starvation by preventing food being subjected to the normal process of digestion. Their growth lower in the intestine may, on the other hand, give rise to obstruction. Besides their mechanical effects, they endanger life by ulceration into neighbouring vessels, causing, it may be, fatal hæmorrhage, by obstructing the outflow of the secretions of the liver or pancreas, and in certain cases by causing perforation into the peritoneal cavity. Simple or infective ulcerations in the stomach or intestine likewise endanger life by hæmorrhage and perforation. Why the perforation of the wall of the stomach or intestine should, as frequently happens, cause death in a few hours is not at all clear. Death is usually attributed to shock, but it is difficult to correlate the phenomena to the two ordinary theories regarding this condition. On the one hand, in a great many cases there is no overfilling of the splanchnic area with blood, and on the other it is difficult to see how acapnia can come into play. An important cause of death from alimentary disease is that due to mechanical interference with the peristaltic functions of the intestine caused by hernia, volvulus, etc. Here again no complete explanation has been given, but there is the possibility of shock playing a definite part in death. The splanchnic area in this case is usually very much engorged, and there is also to be taken into account the pouring out of fluid into the intestinal lumen. The occurrence of perforation subsequent to gangrene of the bowel may play a definite part. Simple obstruction, such as is seen in annular growths of the intestine, may exist for a long period without causing death. A factor in both acute and chronic intestinal disease is the interference with the heart following on the great distension of the abdominal viscera so frequently seen. Death may result from disease of the great accessory glands of the alimentary tract—namely, the liver and pancreas. In the case of the liver, obstruction of the outflow of bile by a tumour or by a

gall-stone leads ultimately to the bile passing back into the tissues, which undergo a slow toxic process due to its presence. Primary disease of the pancreas threatens life chiefly by the effect produced on nutrition through the absence of the secretion of the gland.

The train of events leading up to death may be prolonged and exceedingly complex, especially where a simple defect of a single system is the original starting-point. Whatever the process, however, the final stage consists in the failure of the functions of the lungs and heart. Frequently the commencement of the end is associated with a depression of the vitality of the lung tissue, in consequence of which a pneumococcal affection originates, and thus breaks down the last resisting capacity of the heart. Sometimes, however, the heart itself primarily yields to the final attack of the disease. Usually the act of dying is prolonged over a considerable number of hours, and at the commencement there frequently appear disorders of respiration, which are indications either of oxygen-hunger or of the commencing accumulation of carbonic acid. Alteration may thus occur in the type of breathing, which may assume a Cheyne-Stokes form, or what is described as the "uræmic type." The essential point, however, is a progressive failure of the heart and respiration in which each downward step in the capacity of one system is reflected in a corresponding downward step in the functions of the other. The supply of blood to the lungs by the heart is diminished, and frequently this leads to œdema of the organs. The coating of the alveolar epithelium with fluid interferes with the interchange of oxygen between the air and the blood; the heart is thus supplied with a deficiently oxygenated blood, its inherent weakness is thus increased, and at the same time the respiratory and cardiac centres in the medulla have their controlling functions perverted. The vicious circle established increases progressively in severity of effect, and finally the heart comes to a standstill. Usually long before this happens the functions of the brain are depressed, and unconsciousness occurs. Very rarely consciousness is maintained up till the very end, as is seen in certain very chronic cases of phthisis, and also, it is stated, in tetanus.

While these are the usual phenomena which precede death, in certain circumstances death occurs with unexpected suddenness. Here the heart is primarily at fault. Such a condition may arise in a perfectly healthy individual, usually from reflex causes, such as a blow upon the front of the neck or on the epigastrium; but generally there is some cardiac condition, usually a primary degeneration of the muscular wall or aortic insufficiency. Where the heart is diseased, a sudden exertion on the part of the individual may precipitate the fatal event, which is probably due to a failure of the blood-supply to the cardiac centre in the medulla.

The precise moment of death is difficult to determine, and the signs of death have been much discussed, especially from the

medico-legal standpoint. It has been proved by the application of delicate electrical methods that slight contractions of the heart may go on for some little time after the pulse can be no longer felt or the cardiac signs detected by the stethoscope. Such a heart, if excised and perfused, could beat for hours after the death of the individual. It is certain also that metabolic processes can go on in the body even after the heart has entirely ceased beating. This is evidenced by the results of experiments on surviving organs, and the rise of temperature which is observed after death has occurred, as is seen in certain cases of death from cerebral disease, and in tetanus. There is further evidence of a survival of vital phenomena in many cells, as in the amœboid capacities of the leucocytes, the ciliated epithelium of the trachea, etc., and recent work in which tissues have been cultivated outside the body for many days shows that certain cells can exhibit vital phenomena after the body as a whole is dead.

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